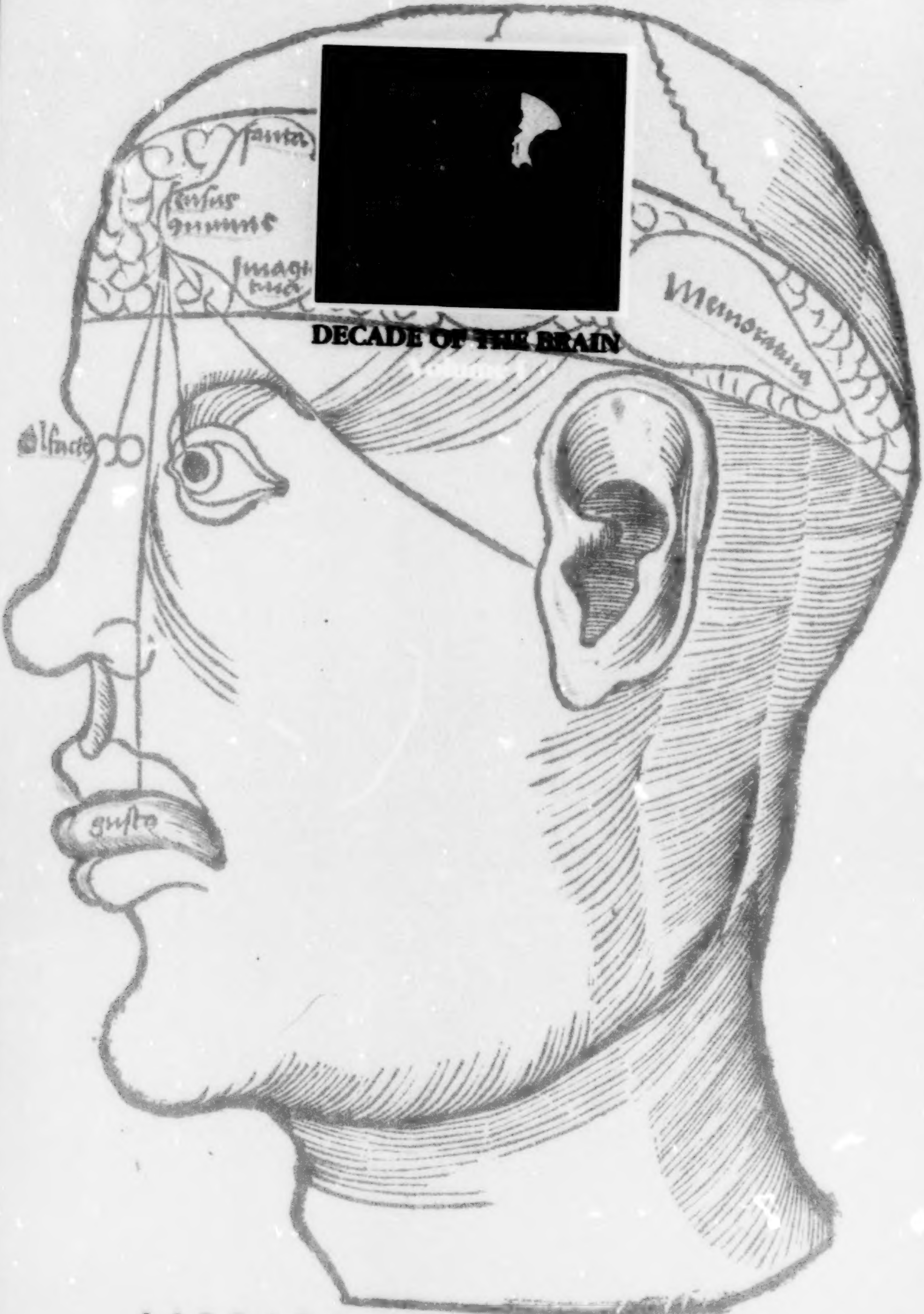
NEUROSCIENCE, MEMORY, AND LANGUAGE



DECADE OF THE BRAIN

Volume 1

LIBRARY OF CONGRESS

NEUROSCIENCE, MEMORY, AND LANGUAGE

DECADE OF THE BRAIN
Volume I

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NEUROSCIENCE, MEMORY, AND LANGUAGE

Papers presented at a symposium series
cosponsored by the
National Institute of Mental Health
and the
Library of Congress

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Volume I

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DEDICATION

Dedicated to the memory of

Silvio O. Conte

of the

United States House of Representatives,

who championed the importance of neuroscience research. He understood that millions of Americans afflicted with brain-related disorders depend on neuroscience research for new treatments or cures. Furthermore, he knew intuitively that it is to the brain sciences that we must turn if we are to maximize human potential. Working tirelessly to promote a joint resolution that gained bipartisan congressional support, he led the effort which resulted in the Presidential Proclamation declaring the 1990s to be the "Decade of the Brain."

The Proclamation stimulates increased public awareness of important scientific advances in this multidisciplinary field.

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PROCLAMATION 6158
DECADE OF THE BRAIN
1990-99

July 17, 1990

By the President of the United States of America

A PROCLAMATION

The human brain, a 3-pound mass of interwoven nerve cells that controls our activity, is one of the most magnificent—and mysterious—wonders of creation. The seat of human intelligence, interpreter of senses, and controller of movement, this incredible organ continues to intrigue scientists and laymen alike.

Over the years, our understanding of the brain—how it works, what goes wrong when it is injured or diseased—has increased dramatically. However, we still have much more to learn. The need for continued study of the brain is compelling: millions of Americans are affected each year by disorders of the brain ranging from neurogenetic diseases to degenerative disorders such as Alzheimer's, as well as stroke, schizophrenia, autism, and impairments of speech, language, and hearing.

Today, these individuals and their families are justifiably hopeful, for a new era of discovery is dawning in brain research. Powerful microscopes, major strides in the study of genetics, and advances in brain imaging devices are giving physicians and scientists ever greater insight into the brain. Neuroscientists are mapping the brain's biochemical circuitry, which may help produce more effective drugs for alleviating the suffering of those who have Alzheimer's or Parkinson's disease. By studying how the brain's cells and chemicals develop, interact, and communicate with the rest of the body, investigators are also developing improved treatments for people incapacitated by spinal cord injuries, depressive disorders, and epileptic seizures. Breakthroughs in molecular genetics show great promise of yielding methods to treat and prevent

Huntington's disease, the muscular dystrophies, and the other life-threatening disorders.

Research may also prove valuable in our war on drugs, as studies provide greater insight into how people become addicted to drugs and how drugs affect the brain. These studies may also help produce effective treatments for chemical dependency and help us to understand and prevent the harm done to the preborn children of pregnant women who abuse drugs and alcohol. Because there is a connection between the body's nervous and immune systems, studies of the brain may also help enhance our understanding of Acquired Immune Deficiency Syndrome.

Many studies regarding the human brain have been planned and conducted by scientists at the National Institutes of Health, the National Institute of Mental Health, and other Federal research agencies. Augmenting Federal efforts are programs supported by private foundations and industry. The cooperation between these agencies and the multidisciplinary efforts of thousands of scientists and health care professionals provide powerful evidence of our nation's determination to conquer brain disease.

To enhance public awareness of the benefits to be derived from brain research, the Congress, by House Joint Resolution 174, has designated the decade beginning January 1, 1990, as the "Decade of the Brain" and has authorized and requested the President to issue a proclamation in observance of this occasion.

Now, Therefore, I, George Bush, President of the United States of America, do hereby proclaim the decade beginning January 1, 1990, as the Decade of the Brain. I call upon all public officials and the people of the United States to observe that decade with appropriate programs, ceremonies, and activities.

In Witness Whereof, I have hereunto set my hand this seventeenth day of July, in the year of our Lord nineteen hundred and ninety, and of the Independence of the United States of America the two hundred and fifteenth.

George Bush

[Filed with the Office of the Federal Register, 12:11 P.M., July 18, 1990]

CONTENTS

Language and the Brain

Preface

This volume is the product of a creative partnership between two distinguished federal institutions—the National Institute of Mental Health (NIMH) and the Library of Congress—which are devoted, each in its special way, to the life of the mind.

The Library, with its commitment to scholarship and to preserving mankind's accumulated wisdom, connects our past heritage with our future possibilities. Enriched by a wealth of holdings in the history of science and by its capacity for critical analysis, the Library provides philosophic and humanistic perspectives on contemporary science for our society and civilization. Comprising both the collective memory of the human race and the creativity that historically has characterized our society, the Library reminds us that intelligent policy requires a commitment to the intellectual life—which today must include a sharp focus on scientific scholarship.

The principal, defining mission of NIMH is to conduct and support state-of-the-art biomedical and behavioral research on behalf of persons with mental illness. In pursuit of that specific mission, NIMH research over the past several decades laid much of the foundation for the now-thriving fields of behavioral and molecular neuroscience supported by it and its sister institutes throughout the National Institutes of Health. Beyond its hands-on scientific responsibilities for brain and behavior research, the Institute exerts public health leadership through its knowledge-transfer programs by providing guidance in the formulation of social policies that will serve individuals with severe mental illnesses. The NIMH's aim is to enhance the opportunities available to all Americans to enjoy the benefits of mental health across their lifespans.

Given these highly individualized yet complementary approaches to the mind and brain, the Library and the Institute welcome this opportunity jointly to introduce members of Con-

gress, their staffs, and the public to the major thrusts of contemporary neuroscience research.

Indeed, the benefits to be gained through a collaborative project involving the Library and NIMH were recognized some years ago, and the seeds for the Decade of the Brain Lecture Series were planted in 1988, even before the late Silvio Conte's vision of a presidentially proclaimed Decade of the Brain was realized. At that time, we laid out the broad outlines and exciting potentials of a joint enterprise designed to strengthen the ties between the scientific community and the Library and, thus, enrich and compound the educational capacities of either operating alone. Our preliminary sketch was refined and expanded by Lewis L. Judd, M.D., NIMH director from 1988 to 1991, and Alan I. Leshner, Ph.D., NIMH deputy director through early 1994, working closely with senior staff of the Library and NIMH. By the time the House Joint Resolution was en route to the White House, whence it would be issued by President Bush as a Presidential Proclamation calling upon all Americans to observe the Decade of the Brain with appropriate programs and activities, planning for the NIMH/Library lecture series was advancing rapidly.

In cosponsoring a lecture series designed to demonstrate and celebrate the progress of science, the Institute and the Library each bring singular perspectives and expertise to the daunting task of educating the public—as well as scientists themselves—about the breadth and directions of a field that today requires well over two hundred specialty journals to report its new developments in the areas of basic and clinical neuroscience. Though the NIMH directs its resources predominantly to the conduct and support of brain and behavioral research, it also has played a leadership role within the federal biomedical research establishment in developing science education programs aimed at keeping the public abreast of the revolutionary advances in brain and behavioral sciences. While the Library regularly responds to requests by the Congress and others for answers to immediate questions and for advice on short-term issues, it also has the capacity to examine thoroughly whole fields that interact with and exert impact on our society and the international community.

The study, treatment, and, ultimately, prevention of mental illness and other brain disorders requires a multidimensional appreciation of the normal course of brain function. In other words, NIMH accountability for attention to mental disorders inherently demands an understanding of the normal brain and its processes, from its genetic and subcellular mechanisms through all intervening

levels of organization, including the study of human behavior across the life span. While such NIMH research delves into basic mechanisms and their expression in pathology, the Institute's union with the humanistic traditions of the Library of Congress reminds us that at the heart of biomedical science is the individual, playing ever-evolving roles in family, groups, the workplace, and society-at-large. This breadth of focus, portrayed effectively in the chapters that follow, encompasses the ethical, philosophical, and policy issues related to brain research and will be elaborated upon in future NIMH/Library of Congress lectures.

The neuroscience revolution, which has added significant impetus to the destigmatization of mental disorders, in many respects derives from an ongoing "revolution" in psychiatry—a sea change in understanding and public attitudes that began with psychopharmacologically derived evidence of the clinical "legitimacy" of major mental disorders. Thus, it is symbolic that the Decade of the Brain, and particularly, this lecture series, coincides with the return of NIMH, after a twenty-five year absence, to its original home at the National Institutes of Health, the premier biomedical research facility in the world. The lecture series, along with the published proceedings, videotapes, and other educational materials prepared by the Library, will advance significantly the process of destigmatization and enlightenment. We further anticipate that broad dissemination of the lectures will help transform the president's Decade of the Brain Proclamation into a wider public understanding of accelerated neuroscience research.

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* Frederick K. Goodwin was director of NIMH from March 1992 to April 1994.

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Foreword

DECADE OF THE BRAIN: THE CHALLENGE OF TODAY FOR TOMORROW

Presidential Proclamation 6158, recommended by a joint resolution of Congress, has declared 1990–99 to be the Decade of the Brain. The neuroscience community has accepted this congressional mandate to pursue a comprehensive study of the nervous system for better understanding basic brain mechanisms in health and disease that affect humankind. We are committed to exploiting opportunities afforded by recent developments in the identification and regulation of cellular functions in the brain that contribute to the multitude of brain maladies, including Alzheimer's disease in the aged, cerebral palsy in the very young, the neurodegenerative disorders of Parkinson's disease and multiple sclerosis, epilepsy, and mental diseases such as the manic depressive disorders.

Beyond its extraordinary potential to heal fundamental human illness, neuroscience, the study of the nervous system and mind, also has implications for the future of American economic competitiveness. Critical industrial technologies of the twenty-first century, such as robotics and intelligent manufacturing systems, will require new research insights to brain function for continued innovation and progress, just as supercomputing has benefitted from the study of parallel information processing mechanisms in the human brain. The undisputed American lead in fundamental neuroscience research can be expected to herald a major competitive advantage to American manufacturers in the next century. Neuroscience, unlike other disciplines in the physical and life sciences, possesses a special ability to contextualize the human species in a larger cosmos and to shed light on what makes humankind unique within the animal kingdom. Francis Crick believes we may be on the threshold of understanding what human consciousness is at a neural level. When we are capable of understanding what human

self-awareness is and how it works, we will have unraveled a critical component of the fabric that makes us human beings. In a sense, we could say neuroscience is the ultimate scientific quest, representing a major contribution to humankind's ever-continuing attempt to understand itself and its place in the cosmos. Indeed, neuroscience has critical implications for the philosophy of man.

The neuroscience community must secure public and congressional support for research equal to the tasks before us if the full potential of the Decade of the Brain is to be realized. To this end, the National Institute of Mental Health (NIMH) and the Library of Congress have combined forces to establish a decade-long lecture series for introducing members of Congress, their staffs, and the public to exciting new theories and breakthroughs in brain structure and function in health and disease as well as in development and aging. These advancements have been obtained, in part, by interdisciplinary research efforts in cell science and technological innovation for the diagnosis and treatment of brain disorders. The interagency effort is intended to encourage public awareness and discussion of the ethical, philosophical, and humanistic implications of emerging brain science of people with healthy brains and minds and for those who are less fortunate.

The NIMH and the Library of Congress are well-matched for a joint endeavor associated with the Decade of the Brain. Since its inception in 1946, NIMH has occupied center stage as the primary federal institution responsible for promoting and supporting research nationwide in the mental illnesses and in the mental health field. Dedicated to improving the mental health of all individuals, fostering understanding, diagnosis, treatment, and rehabilitation of the mentally impaired, and preventing mental illness, the NIMH has been a leader in gaining congressional support for the Decade of the Brain initiative. The NIMH has developed and cosponsored multiple programs with public and private organizations to publicize the revolutionary advances in neuroscience and the benefits anticipated for the more than fifty million Americans burdened with brain diseases and disorders. Additionally, the NIMH has played a pivotal role in fostering science education programs for teachers and students of all ages.

The Library of Congress, founded in 1800, represents the principal educational resource for Congress and an important resource for the public; its services extend well beyond the federal government and affiliated agencies and are readily available to libraries throughout the nation and the world and to all scholars, researchers, artists, and scientists desiring to make use of the Library's

many resources. The Library of Congress is an invaluable depository for materials relating to the study of the nervous system and the history of neuroscience from the era of Hippocrates to the present time.

The series of symposia cosponsored by the NIMH and the Library of Congress are scheduled on a semiannual basis during the Decade of the Brain. The symposia feature presentations by leading neuroscientists, including Nobel laureates, in this country. Their one-day invitational meetings are designed to highlight the discipline of neuroscience and exciting advances from studies delving into the workings of the brain and mind. This forum is intended to provide opportunities for scientists, policymakers, industrial representatives, and other interested groups to discuss potential policy and legislative issues relating to the rapid and dynamic advances in the field of neuroscience. Each symposium is available on videocassette and as a publication, with volume 1 incorporating the first three symposia of the series.

Convened at the Library of Congress in July 1991, the first cosponsored symposium presented an overview of neuroscience advances, including brain imaging technology, artificial intelligence, and the question of human consciousness. The second symposium, held in February 1992, concentrated on learning and memory, the descriptive differences and differing neurological foundations between declarative learning (for instance, the processing of information about people, places, events, and facts) and procedural learning (such as acquisition of new motor skills and perceptual strategies), the organization of memories, and the cell biology of the nerve cell, along with observable results of the strengthening or damaging of connections between nerve cells with memory storage in the brain. The theme of the second symposium emphasized that animal studies and advanced neuroimaging techniques now available clinically have provided significant contributions to our current knowledge regarding how the brain learns and remembers. The third symposium, presented in September 1992, focused on the neural basis of language, including differences between oral, aural, and visual communication systems. This symposium explored the effects of stroke on language processing, how the brain processes visual language (that is, American sign language), scanning techniques for investigating the location of different language functions within the cerebral cortex, and various language functions of the brain recorded from awake patients during brain surgery.

The current decade forecasts a new age for sustained excitement in the exploration of the nervous system and in efforts to

emancipate ourselves from the scourges of brain diseases and disorders. Expanded public awareness and understanding of the issues in the neurosciences through education and research are a prerequisite if the promises of the congressional proclamation of the Decade of the Brain are to be fulfilled. With the first trimester of the Decade of the Brain now past, much has been accomplished on the playing fields of the laboratory and in the halls of private and federal agencies; however, much also remains to be accomplished. We sit on the threshold of important new advances in neuroscience that will yield increased understanding of how the brain functions and of more effective treatments to heal brain disorders and diseases. How the brain behaves in health and disease may well be the most important question in our lifetime.

Richard D. Broadwell

Introduction

NEUROSCIENCE: PAST TO PRESENT

Lewis L. Judd
and
Declan C. Murphy

To introduce this series on the achievements and discoveries of modern neuroscience, the fastest growing area of research in the life sciences, we should set the stage by presenting the historical context of neuroscience. The period of time to be considered extends from antiquity to the beginning of the modern era of neuroscience and the unfolding of brain science through those years. Presenting a whole history of neuroscience in a brief introduction is not possible, but we will focus attention on those brain regions believed to be involved with human cognition, human thought, and, in a sense, human consciousness.

The first real reference to localization of human cognition arose from the writings of Hippocratic physicians of the fourth century B.C., who, with great prescience, wisdom, and some empirical underpinnings, made the statement that essentially all human mental life emerges from the brain. This was a wise statement, for there were a variety of other important organ systems known from which they could have chosen. Only sixty years later Aristotle, the great philosopher and first great empirical biologist, identified another organ system, the heart, as being the repository of human consciousness and thought.

That Aristotle chose the heart rather than the brain set into motion a controversy that extended throughout brain science for the next two thousand years. He assigned to the brain a secondary role as a cooling organ, a counterpoint to the heat emerging from the vital life force responsible essentially for all higher human cortical function that resided in the heart.

Galen, the last of the great research physicians of antiquity, placed human cognition where it belonged, in the brain. Galen believed, based on animal dissection, that the brain was responsible for all mental activity, for reasoning, for the repository of the

Figure 1. "Animae Sensitivae," a woodcut illustration from Gregor Reisch, *Margarita Philosophica* (1503), shows a medieval diagram of the brain. (Rosenwald Collection 595, Rare Book and Special Collections Division, Library of Congress)

senses, and for the repository of memory. At this point the brain was identified as the organ system involved in human cognition.

For the next hundreds of years, through the Middle Ages, church scholars and interested research physicians agreed with Galen that the brain was involved in human cognition. However, the cavities of the brain or the brain's ventricular system, not the substance of the brain, were considered the repository of human thought and consciousness. The first illustration of the brain recorded in Western thought was from an eleventh-century manuscript which conceptually depicted the predominant organ systems in human physiology: the heart, the liver, the testes, and the brain. The medieval concept of the brain believed the brain to be divided into three separate compartments, to each of which were ascribed specific mental functions. A nonanatomical diagram shows the front compartment, called the sensus communis, receiving all of the input from the senses and giving rise to fantasy and imagination.

The second compartment, in the middle, was believed to give rise to rational thought and reason, and the third compartment represented the repository of memory. The vermis, the only allusion to an anatomical structure, was viewed as a functioning valve between the first and second compartments (figure 1). This interpretation for the predominant theory of the brain and brain function persisted through medieval times.

Vesalius, the great research physician of the Renaissance, initiated a tremendous leap forward in the thinking about the brain by providing an accurate anatomical drawing based on his dissections of the human brain, representing its two lateral ventricles. He refuted the cell doctrine and established once and for all that the locus of human thought and consciousness resided within the substance of the brain.

Over the next 250 years research physicians, scholars, philosophers, and church scholars brought forth a number of candidates within the brain as the locus for that aggregate of higher human cortical functions we call the soul. In 1649, Descartes indicates in the *Passions of the Souls* that the soul exercises its function not in the heart, again reacting to the strong influence of Aristotle well over two thousand years before, but in the brain. The soul was not necessarily in the total substance of the brain but in a small gland in the center of the brain, which we now refer to as the pineal gland.

Cortical localization received its next great step forward approximately 250 years later in the school of phrenology with Franz Joseph Gaul. Gaul and his followers felt that the location of human mental activity was in the cerebral cortex of the brain. They believed incorrectly that dozens of tiny centers on the very surface of the cortex increased in size through mental activities and were manifested as bumps on the skull. Phrenologists assigned specific mental functions to these bumps and believed one could analyze a person's character by examining the bumps on the skull.

Phrenology was an interesting phenomena in that, although the hypothesis and the premises were largely wrong, both were correct scientifically to point the research scholars of the next 150 years to the human cortex as the site of human cognition and consciousness. Many of the pioneers of neuroscience, like Brodmann, Sherrington, Spencer, Jackson, Cushing, Krause, and Penfield, all focused on the human cerebral cortex in an attempt to localize precise mental function.

One notable effort was made by Brodmann and his workers in the early part of the twentieth century; they divided the cortex into

fifty-two different areas, each assigned a specific site for certain types of mental function. These cortical areas have been refined by research since that time, but we still use the Brodmann areas as points of reference for localization in the cortex. The work of Canadian neurosurgeon Penfield and coworkers basically culminated in the discreet mapping of the cortex by their clinical studies with patients.

To recapitulate, actual progress in neuroscience and brain science until the twentieth century moved rather slowly. The six hundred years from Aristotle to Galen established the brain as the site of human cortical higher function. An additional thirteen hundred years, from Galen to Vesalius, were required to realize the existence of a substance, unassociated with the ventricular system, that was involved with brain functions. Several hundred years later, the cerebral cortex was identified as the actual site of higher cortical function.

Why was such progress so slow? Consider the sheer complexity of the organ system we call the brain, with its more than 100 billion interconnected neurons and brain cells. Think of the brain's inaccessibility. Because of its enormous importance, the brain has been protected by evolution; it exists in a bony helmet, the skull, and sits in its own hydraulic water bath for protection from shock. The brain is shielded by the blood-brain barrier from circulating toxins to which the rest of the body may be exposed. The technology that begins to give us access to the brain and its functioning has become available only recently.

Brain research is very different from virtually all other areas of science insofar as the data emerging from it have a very heavy impact on our concept of human consciousness, our concept of who we are as human beings, and even, in a sense, of our place and our uniqueness in the cosmos. As information emerges, brain science often finds its discoveries interwoven with philosophical and religious dogma of the day, which influences the interpretation and the acquisition of these data.

A new era of neuroscience began some thirty-five to forty years ago when the technology and principles of modern biology, especially molecular and cellular biology, began to be systematically turned to what was then the last wide open frontier in biomedical research, the brain. This new attention has fueled a revolution in our understanding of the brain and how it functions.

The National Institute of Mental Health has calculated that 90 percent of what we know about the brain has been learned in the last ten years. As partial support for this idea, a simple frequency count was done of scientific articles with the word *brain* in the title. Ninety percent of the scientific articles with the word brain

in their titles were published in the 1980s. The same holds true for the term *neuron,* designating the basic functional and cellular unit of the brain. The same is true for the word *neurotransmitter,* which describes chemical substances allowing neurons to communicate or "talk" with each other.

What helped fuel this revolution in neuroscience? We have borrowed heavily from other scientific revolutions. For example, molecular biology, with the identification of the structure of DNA (deoxyribonucleic acid) and the ongoing characterization of its function within the body, has opened a whole variety of areas for research in molecular genetics. Calculations suggest that about 35 to 40 percent of all the genes in the human genome are focused on the structure and function of the brain.

A revolution has increased the ability of science to image the brain and access information on the brain. We have entered an era where on a routine basis we can obtain accurate detailed pictures of the brain structure and actually watch a living human brain while it is functioning. A revolution in computer science has occurred simultaneously, which has enabled neuroscience research to search for answers to questions we would not have dreamed of asking ten years ago. This particular revolution has allowed us to model brain function through computers, one of the most elegant examples of which has been contributed by Gerald Edelman, who has constructed an automaton that explores its own environment.

In conclusion, the confluence of the revolutions and developments of other fields have fueled neuroscience development to the point where the time now is appropriate for us to direct attention to a true decade of the brain.

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Abbreviations

AI	Artificial intelligence
ASL	American Sign Language
BDAE	Boston Diagnostic Aphasia Examination
CT	X-ray computed tomography
DNA	Deoxyribonucleic acid
EEG	Electroencephalography
ECo	Electrocorticography
ECoG	Electrocorticogram
EM	Electron microscopy
ERP	Event-related potentials
fMRI	Functional magnetic resonance imaging
IQ	Intellectual ability
LHD	Left-hemisphere damaged
LTP	Long-term potentiation
MEG	Magnetoencephalography
MR	Magnetic resonance
MRI	Magnetic resonance imaging
NMR	Nuclear magnetic resonance; now called MRI
PET	Positron emission tomography
PETT	Positron emission transaxial tomography
RHD	Right-hemisphere damaged

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BRIGHT AIR, BRILLIANT FIRE: NEUROBIOLOGY AND THE MIND*

Gerald M. Edelman

My friend, the late Leo Szilard, a great physicist, had, among his other accomplishments, the foresight to propose to Albert Einstein that he write to President Roosevelt about the urgent need in wartime to construct an atomic bomb. Thus began in dire times the realization of a close embrace between science and politics in America. The issues resulting from that embrace have been many. Among them were a remarkable system of funding basic research and a mounting understanding of ethical issues as they relate to science and society. Times now are not quite so dire, but they are interesting enough to reflect on that continuing embrace and what its new issue might be.

My remarks are concerned with brains, computers, and consciousness. My thesis is this: if nuclear physics was in one sense a culmination of a remarkable trail of research, the flowering of current brain science will be an even greater one—one that will transform both science and society in fundamental ways. How do we approach the brain, the most complicated of material objects with its 10^{15} neuronal connections, the tangible source of what might be called the mystery above the neck? The short answer is "with every approach conceivable," for brain science is the most multidisciplinary of all sciences. What is notable is that its various disciplines are beginning to flow together. Along with this confluence, we have witnessed an enormous growth in knowledge. More has been learned about the human brain in the last two decades than in all of human history. But however much we have learned (and I will talk about that shortly), it is well to remember that, of all organs, the brain is the center of human concern. To know how kidneys are made will probably answer 99 percent of the questions

* The phrase "Bright Air, Brilliant Fire" is from a fragment of Empedocles, the fifth-century B.C. materialist philosopher of mind. It reads:
For by earth we see earth, by water water, by air bright air, and by fire brilliant fire.

concerning how brains are made, but brains are unique in the all important remaining 1 percent—they are the source of how we know, the fountain of epistemology.

At the great dawning of the modern age, the importance of the brain to the body began to be understood. Indeed, the Enlightenment which took over Europe in the eighteenth century reflected this understanding. This great union of reason, science, and politics spawned three political revolutions—the English Civil War and the American and French Revolutions—within somewhat more than one century. The science underlying the Enlightenment was physics—the physics of Newton, Galileo, and Kepler. Great explorations, a dawning secularism, and a passion for democracy are left with us as a consequence. But even at the dawn of the Enlightenment, there was a suspicion that brains were at the center of what was essentially human. I might remind you that Diderot, the great Enlightenment genius and coauthor of the *Encyclopedia,* writes amusingly and even penetratingly on the subject.

Where have we come since the Enlightenment? Into a rich time of knowledge, into an audacious set of possibilities hinted at by neuroscientific research, indeed into the likelihood of a revolution in science itself. Let me just mention a few of the medically significant achievements. They include, among others, a pharmacological revolution that has transformed psychiatry, a specific set of insights into degenerative brain diseases such as Parkinson's and Alzheimer's diseases, a mounting mastery of the microanatomy of the brain, a triumphant entry of neurophysiology into the actual bases of perception, and an alliance between chemistry and molecular biology that opens the possibility of diagnosing precisely and coming to grips with genetically based brain disorders. I might add that to this diagnostic armamentarium have come the large guns of brain-scanning techniques. When they are perfected and their resolution for the detection of small regions of tissue are enhanced, they will revolutionize neurology and basic research into brain functions as well.

These achievements presage a revolution in medicine, one to which the National Institutes of Health have contributed vastly—a revolution of which they may rightly be proud. All these accomplishments call for common sense and, above all, for judgments that go beyond those of the laboratory.

This progress provides my first theme, which is concerned with significant approaches to brain disease. It is a theme that is as obvious as it is important. The results of research progress will in-

fluence not only brain science but also other medical arenas, for the brain is the master gland and controller of other body organs.

I want now to mention a second theme, one which is not so obvious but which may be of even greater significance, for it bears on how we know and perceive. This theme is concerned with the relationship between the brain and computers. Let me begin by stating most emphatically that the idea that the brain is a computer, which is currently bandied about, is only slightly less fatuous than the proposal that the world is a piece of computer tape. Were this idea correct, we might be tempted to condescend to politicians even more than we are now tempted to do, even when we take into consideration their endlessly complicated and arduous task. After all, why don't they just read the tape in order to know what to do? But, as they know only too well, the world is open-ended and we need more than computers and computer metaphors in order to govern effectively.

Now I don't wish to be misunderstood. Computers are the most interesting inventions of the twentieth century, and they do something that it takes brains to construct. That something is logic. Computers are logic engines—any problem that can be clearly described in logical terms can be solved in principle by a computer. When, as a student at the University of Pennsylvania, I heard of our first practical digital computer, ENIAC, housed in the Moore School, I did not imagine the myriad uses and the trillion- dollar potential of such engines. They are now central in our scientific enterprise and in human affairs, and American leadership in their development constitutes one of the great scientific achievements of our time.

But computers do not perceive. With the help of our bodies, brains do. I like to ask my friends in the artificial intelligence community to make a choice: Assume you are going hunting for birds in a swamp in bad weather. I offer you the choice of a new version of the latest Air Force computer in a tea cup, a friendly version that speaks English, or a dog. Which would you choose? The computer or a well-trained bird dog? Most people, even those working in artificial intelligence, pick the dog. The reason is not difficult to tell. The dog perceives novelty, the computer does not. Events in swamps are not exhaustively programmable, except perhaps in a boring way by frogs.

I now arrive at the audacious part of my second theme. Is it possible that, besides embodying logic in a machine, we could embody other brain functions as well? Is it possible to build a perception machine, for example? I think the answer is yes and that

theoretical developments in brain science are proceeding toward substantiating that conclusion. Work on this question at the Neurosciences Institute in La Jolla, California, is certainly quite promising. If realized, perception machines will be of the utmost significance. Even without the ability to perceive, computers have transformed the modern world. Suppose that computers could be coupled to new devices that could perceive—or that could at least carry out many of the functions of perception—devices that instead of being programmed, would be trained. The prospect is staggering and the economic consequences, if such a development were realized, would be enormous.

America finds itself in the best position of any nation to embody the emergent understanding of higher brain functions in such new devices. The United States leads in the burgeoning field of neurosciences and it remains the leader in computer technology. It is just this combination that is necessary to develop perception machines. Others pride themselves on living in the robot kingdom. We should pride ourselves on using the combination of neuroscience and computational resources imaginatively again to extend the powers of the human brain. Such a combination will not only bring great benefits commercially but will further our basic understanding of higher brain functions, those that make us human, that allow us to be what we are. For those of you who are skeptical, I only ask you what your position would have been in 1900 if I described the possibilities and performance of personal computers.

Now, to the third of my themes. I have talked of brain disease, and I have talked of the great insight and technological potential that an understanding of higher brain functions will bring, especially if we use the computer not as a model of the brain but as a tool for envisioning how the brain works. These are thrilling and important arenas. In my third theme, I want to talk of the brain's greatest product, the mind, or human consciousness itself. There are some who would say that to go into this arena is foolhardy, that brain science should limit itself to questions related to the brain itself and avoid metaphysical problems. The argument goes that one can ask one question too many and that may be embarrassing. I do not agree, despite the risk.

The reason I think scientists should ask all the questions we can about the mind is that the brain is the organ of the mind, the organ of speech and thought, the organ of politics and of human individuality. Indeed, recent studies of brain development suggest that no two brains are alike and that this fundamental biological diversity is important to recognize in law, in education, and in our

common pursuit of the idea of progress. This idea, I believe, will be nourished by neuroscientific discovery.

The idea of progress has been central to this country's history and remains central to our future. It is the key idea underlying the public support of research. Two main ingredients of progress, as pointed out by Professor Nisbet of Columbia University, are the belief in the gradual but inexorable growth of human knowledge and the belief in the possibility of our moral improvement. Both of these notions have concerned us in our search for better ways of supporting science in the public interest. Just as our preeminence in physics depended on an enlightened interaction between the government and the scientific community, so will the realization of the enormous promise of American neuroscience depend on additional and new modes of support.

I believe that we need to establish a new task force to encourage enlightened interactions that are dedicated to the further development of brain science. After all, the brain is special, the promises of brain research are greater—and the moral issues even more challenging—than in practically any other area of scientific research. I would like to suggest that besides supporting existing agencies dedicated to brain research, such as those of the National Institutes of Health, the government consider the formation of a Brain Task Force for the Decade of the Brain. This task force should attempt to delineate the relative importance of the problematic choices that we will have to confront as we begin to understand the brain as the basis of the mind. In addition, the task force should certainly concern itself with brain disease; it should probably develop a special initiative in perception machines; it should absolutely be concerned with efforts to inform the American public about the development of brain science as a national target in the decade to come.

The Enlightenment, which flowered in the eighteenth century and which gave us so much, including the idea of modern democracy, is over. Its underlying science was physics and its world view was taken from the notions of physics. But we recognize that since the turn of the century the view of a world machine has been supplemented by another view, provided by theoretical particle physics and by Darwinian theories of biology. This view has not yet fully penetrated people's thinking, even after a century. Its implications are not at all those of a world machine, inexorably grinding on to an inevitable outcome. Modern field theory in physics and modern evolutionary theory simply do not support such a notion. To recognize this grounding in a global scientific

world view resting on physics and biology is important. This recognition affects our hopes and our bases for behavior.

Henry Adams, the scion of the great Adams family, in his book *The Education of Henry Adams*, took a gloomy view of the contrast between the Virgin of the Middle Ages and the Dynamo as a symbol of modern technology. We can be more sanguine than he was. We are now in an extraordinary period of history, one of major social and ideological reformation, one of enormous economic change and promise. This period is no less exciting than that which spawned the American and French Revolutions. What is distinctive about the present revolution is that it is not so far grounded in persuasive ideas but rather in the outcome of enormous changes in communication. But revolutions need ideas. I believe now the stage is set for a Second Enlightenment, and I believe that rather than physics, the underlying science of this Enlightenment will be brain science. And, unlike the first Enlightenment, the second one will, for this reason, be able to translate humanistic theory into practice. What was lacking the first time was an understanding of how our brain actually works to create sciences like physics and also to help govern our interactions in society.

It is notable that Congress, in 1990, passed a joint resolution and that President Bush affirmed the decade of the nineties to be the Decade of the Brain. We, as neuroscientists, welcome this as a most promising and imaginative step. We look forward to the realization of its promises in terms of increased support for existing agencies in the National Institutes of Health, in terms of the possible creation of a Brain Task Force, and in terms of emphasizing public recognition of the central human and economic importance of research on the brain. This realization will reflect our need to race to the new frontier as a leading nation, a nation which is used to such progress, and one indeed with a history symbolic of such pushes to the edge of existing frontiers. Just as one can ask one question too many, however, one can pronounce too much. I hope I have not done so here and hasten to summarize what I have said.

The scientific community needed the proclamation of the nineties as the Decade of the Brain. But on this occasion I want to go further in my projections. I suggest that with the proper support, the new century following that decade will witness America's second great achievement in the unfolding of humanity's dream of progress—the pursuit of individuality in a meaningful life within the human community, one made meaningful by the noble pursuit of knowledge about the biological bases of our very humanity. Should we emulate our best past efforts in ensuring that the governmental

support of science proceeds in an enlightened fashion, we may even live to see the dawning of a Second Enlightenment.

A knowledge of brain science will provide one of the major foundations of the new age to come. That knowledge will spawn cures for disease, new machines that are based on brain function, further insights into our nature and how we know. There is no better ground for hope in things human. My personal hope is that we in America can play the leading role in the enterprise. The Decade of the Brain is an auspicious beginning, and I congratulate our lawmakers and the president for bringing it to pass.

Suggested Reading

Bruner, J. 1990. *Acts of Meaning*. Cambridge, Mass.: Harvard University Press.

Changeux, J.P. 1986. *Neuronal Man: The Biology of Mind*. New York: Oxford University Press.

Edelman, G.M. 1987. *Neural Darwinism: The Theory of Neuronal Group Selection*. New York: Basic Books.

Edelman, G.M. 1989. *The Remembered Present: A Biological Theory of Consciousness*. New York: Basic Books.

Edelman, G.M. 1992. *Bright Air, Brilliant Fire*. New York: Basic Books.

Mayr, E. 1982. *The Growth of Biological Thought: Diversity, Evolution, and Inheritance*. Cambridge, Mass.: Harvard University Press.

Reeke, G.N., Jr. and G.M. Edelman. 1988. Real brains and artificial intelligence. *Daedalus* 117, no.1 (Winter): 143–73.

Sacks, O. 1993. Making up the mind. *New York Review of Books* 40, no.7 (April 8): 43–49.2.

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10

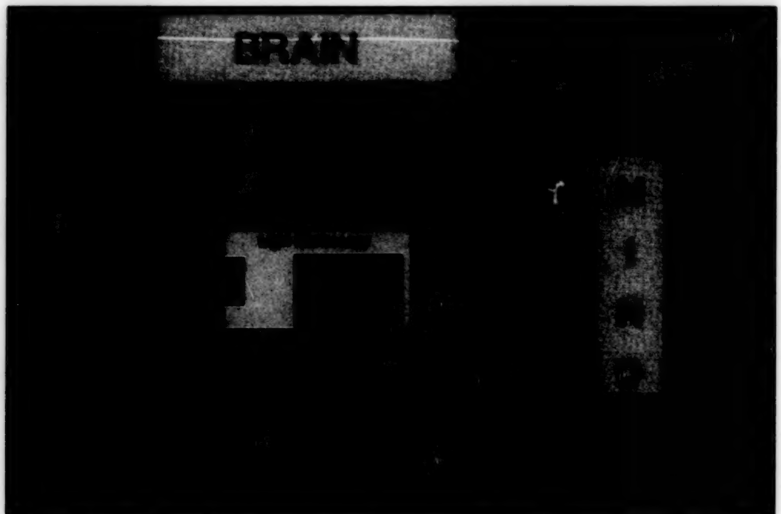
SEEING THE BRAIN IN ACTION THROUGH BRAIN IMAGING

Marcus E. Raichle

One of the greatest scientific challenges of our time is understanding the relationship between the human brain and human behavior. Greater understanding should provide a more rational basis for our comprehension of some of the most devastating human diseases and for their treatment. Such understanding should also enlighten us about the solution to the problem of mind-brain interaction that has intrigued us for so long.

As the result of major technical advances, neuroscientists are equipped with a large number of tools to explore the brain and its relationship to behavior (figure 1), but relatively few of these tools are applicable to the study of the human brain *in vivo*, especially the normal human brain (figure 2). The human brain is ultimately what we strive to understand. Work in other neurobiological systems must, therefore, be related to the human brain. Further, some uniquely human processes such as language and its disorders and certain diseases (e.g., schizophrenia) can be studied only in humans. Modern brain-imaging techniques are among the tools uniquely suited to help bridge the gap between advances in nonhuman neurobiology and human behavior and also to provide insights into functions and diseases uniquely human.

During the past two decades safe techniques for obtaining images of the living human brain have become widely available in research and clinical medicine. This revolution in diagnostic imaging began with the development of X-ray computed tomography (CT) in the early 1970s, followed by positron emission tomography (PET) and nuclear magnetic resonance (NMR, now usually referred to as magnetic resonance imaging or MRI). Each has made special contributions: CT and MRI to the production of refined, in vivo, anatomical images, and PET to images of brain function measured in terms of local pharmacology, chemistry, acid-base status, metab-



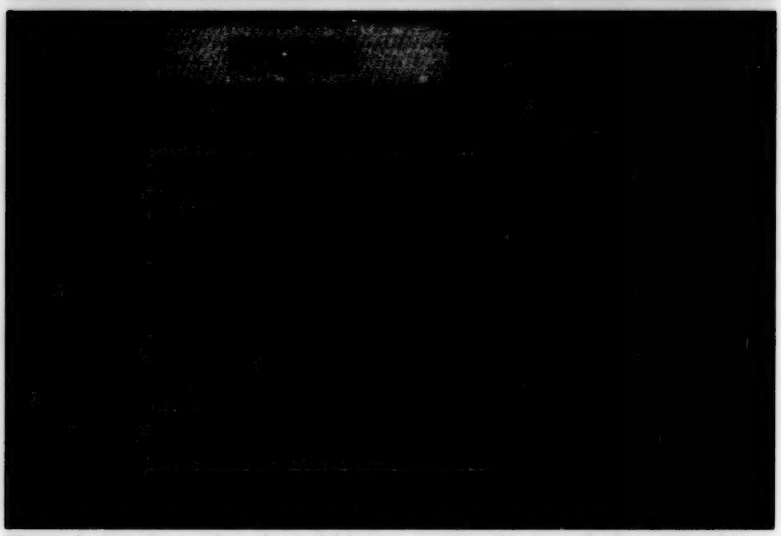


Figure 1. *(top)* Research tools available to neuroscientists to study the relationship between the brain (here defined as a structure occupying space) and the mind (here defined as events occurring in time). Here the brain is represented along the horizontal axis in a logarithmic scale in terms of spatial resolution and ranges in magnitude from an object the size of the whole brain on the top to an object the size of a molecule on the right. The mind or behavior is represented along the verticle axis, also in a logarithmic scale but in terms of time and ranges from an average human life span on the top to a fraction of a second on the bottom. All of the tools available for the study of anything from molecules to intact humans are depicted here in terms of their temporal and spatial resolutions.

Figure 2. *(bottom)* Depicts only those tools available for the study of the living human brain. The following abbreviations are used: electroencephalography (EEG); event-related potentials (ERP); electron microscopy (EM); electrocorticography (ECo); magnetoencephalography (MEG); and positron emission tomography (PET).

olism, blood volume, and blood flow. In this review I will focus on the contribution that PET can make in understanding the *function* of the normal human brain.

Positron Emission Tomography (PET)

Emission tomography is a nuclear medicine technique that produces an image of the distribution of radioactivity in the human body, resulting from the administration of substances containing radioactive atoms. PET uses the unique properties of radioactive atoms, which decay by the release of positively charged particles called positrons, to provide an image that is a highly faithful representation of the spatial distribution of radioactivity in selected planes through the tissue. The radioactive atoms most frequently employed in PET are atoms with very short half-lives and, with one exception (fluorine-18, half life 2 hours) these are atoms commonly used in the body's physiological processes, such as oxygen-15 (122 seconds), nitrogen-13 (10 minutes), and carbon-11 (20 minutes). Ingenious labeling techniques permit radiochemists to incorporate these atoms into compounds used normally by the brain, such as glucose, oxygen, and various drugs. Investigators can then monitor a variety of processes in the human brain. A discussion of the sophisticated mathematical techniques by which PET measurements of tissue radioactivity are converted into quantitative cross-sectional maps or local blood flow, metabolism, or other variables is beyond the scope or intent of this review. Several general discussions are noted in the suggested reading.

Monitoring Behavior-Related Changes in Brain Function by PET

The window through which we examine the functional organization of the normal human brain with PET is based upon our ability to measure neuronally induced changes in local blood flow within the tissue. Interest in the relationship between local brain blood flow and local functional activity has spanned nearly a century. The initial interest crystallized when, in 1890, two famous British scientists, Roy and Sherrington, published the seminal paper in which they suggested that an "automatic mechanism" exists that provides for a local variation in blood supply in accordance with local variations in the functional activity of the brain. Subsequent experiments in laboratory animals and humans led to confirmation of these pioneering observations and to the establishment of one of our most sensitive and accurate means of studying the functional anatomy of the normal human brain in vivo. Reliable estimates now

indicate that changes in neuronal activity locally in the brain are accompanied by rapid (<1sec) changes in local blood flow, and PET accurately and rapidly measures such changes. Assuming all mental activity is accompanied by changes in local blood flow, PET is well suited to accomplishing the task of relating changes in local neuronal activity to mental activity.

The Basic Functional Anatomy of Mental Activity

Substantial evidence, largely obtained from the study of brain lesions such as strokes in humans, supports the hypothesis that the human brain is structurally and functionally modular. Modularity here refers to the assignment of specific components of a particular mental activity—for instance, telling someone else the meaning of a word that has been read recently—to different areas of the brain. Thus, such an act might require, at a minimum, visual attention, perception of the simple visual features of the word, word recognition, short-term memory to hold the word on-line while its meaning is accessed, interrogation of the mental lexicon or library of appropriate meanings, development of an appropriate motor program to activate and coordinate the muscles of speech and, finally, execution of the program in the act of speaking. We further assume that these various components or "computations" of the mental activity of interest are carried out in different parts of the brain in local ensembles of neurons or information-processing modules. The *coordinated activity* of these distributed modules or local ensembles of neurons results in the observed behavior. At the heart of the efforts to understand the workings of the normal human brain with PET is the attempt to begin the process of estimating the number of such components and assign them to specific regions of the brain. With such functional "maps" we should eventually be able to determine how discrete modules or ensembles of neurons representing specific computations are harnessed in the execution of normal mental activities; determine more precisely the functional impact of localized lesions; and hypothesize more intelligently about the functional anatomy of diseases with unknown neuropathology (e.g., various learning disabilities such as dyslexia, attention deficit disorder, depression, or anxiety). Such an understanding of the general brain organization of mental activity must at least accompany, if not precede, a knowledge of how specific components of mental operations are implemented in individual modules or local ensembles of neurons. It is the ability of PET measurements of local blood flow to accurately identify and study

widely distributed component modules supporting specific mental operations that makes PET such a valuable tool in developing an understanding of the distributed modular relationships underlying mental activities in the human brain. Recently, similar measurements also have been made with MRI.

The Strategy

The strategy for the functional mapping of neuronal activity in the human brain with PET consists of a number of important elements. These include the deliberate selection of blood flow as the most accurate and flexible signal of changes in local neural activity that can be detected with PET. To begin the process of isolating and identifying important regional changes in blood flow related to a specific mental activity, images of blood flow in a carefully selected control state are subtracted from images obtained during the desired activity in each subject. This is known as paired image subtraction. The control state and the stimulated state are carefully chosen so as to isolate, as far as possible, a single mental operation. By subtracting blood flow measurements made in the control state from the task state, we can identify those areas of the brain concerned with the mental operations unique to the task state. This extends to our work a strategy first introduced to psychology by Donders in 1868, in which reaction time was used to dissect out the components of mental operations. In our work we can now do so in terms of specific regions of the brain. These subtraction images form the basis of a data set composed of averaged responses across many individual subjects or across many runs in the same individual. Image averaging dramatically enhances the signal-to-noise properties of such data. This enables us to detect even low-level responses associated with quite subtle mental activity. To illustrate the use of this strategy, I will discuss work designed to allow us to understand the functional anatomy of normal human language.

Functional Maps of Normal Human Language

One of the unique features of humans is their capacity for communication through a formal spoken and written language. Beginning with the pioneering work of Pierre Paul Broca and Carl Wernicke in the last century, substantial evidence from damaged brains (e.g., from strokes) suggests this unique capacity is the result of the contributions of specialized brain regions primarily in the left hemisphere of most right-handed individuals.

For several years now we have been examining the cortical anatomy of single-word processing as an initial step in the study of

language in normal individuals. Because of the great complexity of language, restriction of our initial efforts to an understanding of the processing of individual words seemed warranted. Furthermore, the design of tasks appropriate for such studies with PET was greatly aided by extant knowledge in cognitive psychology, linguistics, and clinical neurology.

In our initial work we used four behavioral conditions in each subject to form a three-level additive hierarchy in which each task state was intended to add a small number of mental operations to those of its subordinate (control) state. The general results of this study are summarized in figure 3 and described in more detail below.

In the *first-level* comparison, the visual presentation of single words without a lexical task was compared to visual fixation of the small cross hairs on a television monitor without word presentation. Words were presented for 150 msec at the rate of once per second on a television screen during the 40-second measurement of blood flow. No motor output or volitional lexical processing was required in this task; rather, simple sensory input and involuntary word-form processing were targeted by this subtraction.

The areas of brain identified as active during the passive viewing of words appear to support two different computational levels, one of passive sensory processing in the primary visual cortex and a second level of modality-specific word-form processing in visual association areas. The main regions activated (figure 3) were in primary visual cortex bilaterally and visual association areas. The primary visual cortex responses were similar to those produced by simple sensory stimuli such as a simple flashing checkerboard. The regions in association cortex became candidates for a network of cortical modules that code for visual word form. Subsequent experiments (figure 4) demonstrated that an area located just in front of primary visual cortex was activated by words and pseudo-words (e.g., cade, snegard), both of which obey the pronunciation rules of the English language (i.e., they are orthographically regular), and not by consonant letter strings or false fonts (i.e., symbols with all of the visual features of letters grouped together as in words; see figure 4). Taken together, a unique ensemble of regions in the striate and extrastriate cortex activated by passive visual words and pseudowords appears, functionally, to analyze visual symbols and distinguish between those that behave according to rules of the English language (for native English-speaking subjects) and those that do not (figure 5). The location of such a specialized network of information-processing modules more precisely defines the system damaged in acquired pure word blindness (a condition in which patients

can read letters but not recognize words) and the possible locus of difficulty in patients with reading disabilities such as dyslexia.

When hearing words, subjects activated an entirely new set of areas distinct from those activated by looking at words (figure 3). Only when subjects were asked to judge whether pairs of visual words rhymed were responses seen in *both* visual and auditory word perception areas simultaneously. This particular observation emphasizes the functionally flexible nature of these modular relationships (figure 5).

In the *second-level* comparison, subjects were asked to repeat the words they saw or heard. The control state for the PET blood flow subtraction was the passive presentation of auditory or visual words. Areas related to motor programming and output were activated (figure 3). In general, similar regions were activated for visual and auditory presentation. Thus, different inputs (e.g., visual and auditory) converge on a single output system.

In the *third* and final *level* of comparison, subjects were asked to speak a verb for each seen or heard noun presented. Responses were identified in three areas of cerebral cortex and the right cerebellar hemisphere (figure 3). The areas of the cerebral cortex included a region in the left frontal cortex; a frontal midline region in an area known as the anterior cingulate gyrus (not shown); and the posterior temporal cortex (not shown). We hypothesize that the responses in the anterior cingulate cortex are part of an anterior attentional system engaged in selecting the appropriate response from among competing alternatives. The role of the left frontal cortex is less clear but may contribute to the short-term memory required to perform the task. Because of the proximity responses in the left temporal cortex to Wernicke's area, we would suggest that this area is concerned with the conscious semantic aspects of the tasks (i.e., looking up the meaning of the word). Further experiments will be needed, however, to clarify the true role of these and other areas engaged in the task.

Responses in the right lateral cerebellar hemisphere were also detected in this task (not shown in figure 3). Because we had subtracted the motoric aspects of simply saying words, this result strongly suggests that the cerebellum (traditionally thought to guide motor activity) plays an important role in high-level information processing involving a task that engages the left prefrontal cortex. In support of this hypothesis, we have recently had the opportunity to study an individual with a stroke confined to the right cerebellar hemisphere. At the time of our examination the subject had recovered from the motor signs of his stroke and appeared normal on

Figure 3. Maps of changes in local brain blood flow in the normal human brain during the processing of words. By averaging positron emission tomography (PET) images it is possible to isolate cortical regions concerned with the processing of words. The four lateral views of the human brain shown here are averages of the brain activities of nine normal subjects. The input components of language—visually scanning a word or hearing it—activate the regions of the brain in the upper two images. The output components of language and the thoughts stimulated by this activate the regions shown in the lower two images.

The upper right depicts the regions of the brain active while reading common English nouns one at a time at the rate of one per second. Responses are observed in the primary visual cortex and visual association cortex. The control state for this scan is simply looking at the blank television monitor upon which the nouns had been presented.

The upper left shows the regions of the brain active while hearing common English nouns pronounced one at a time at the rate of one per second. The same words used in the reading task were used for this listening task. The spoken word activates an entirely different set of areas than the read word. These occurred in the temporal cortex and at the junction of the temporal and parietal cortex.

At the lower left are shown the regions of the cortex that are active while speaking. Subjects were presented with words, either spoken through earphones or displayed on a television screen. (The visual and auditory activity that occurred when the subjects simply read or heard the words has been subtracted from the active responses seen in this image.) Speaking a word activates the primary motor cortex, the supplementary motor cortex (not shown), the cerebellum (not shown), and an area over the Sylvian-insular cortex. Thus, both visual and auditory pathways converge in this network of areas, the system concerned with motor programming and output.

At the lower right is the anterior, inferior frontal cortex, hich becomes active during such mental operations as consciously analyzing the meaning of a word. In this instance, subjects were asked to respond to seen or heard words (common English nouns) with the first appropriate verb or action word that came to mind (for example, the word *hammer* might elicit the response *hit*). The visual and auditory activity that occurred when the subjects read or heard the words as well as the motor system activity resulting from responding have been subtracted away.

Figure 4. Maps of *changes* in local brain blood flow in the normal human brain while viewing words and word-like forms. By averaging positron emission tomography (PET) images it is possible to isolate cortical regions concerned with the processing of words. The four views of the human brain shown here are averages of the brain activity in nine subjects. The particular view of the brain shown here is along the inner surface of the left cerebral hemisphere. The objective of this study was to determine if words or word-like symbols are uniquely processed by the brain. The strategy was to present stimuli of increasing levels of complexity and compare the responses.

In A subjects passively viewed computer-generated false fonts that contain all of the visual features of letters and words (i.e., the same number of lines, angles, units, etc.) but do not contain true letters, cannot be pronounced, and do not convey meaning. An example of a typical stimulus is shown above the image.

In B subjects passively viewed consonant letter strings, arranged like words of varying lengths. In this instance the letter strings could obviously be recognized as groups of letters and contained the same basic visual features as the false fonts but did not follow the pronunciation rules of the English language and conveyed no meaning. An example of a typical stimulus is shown above the image.

In C subjects passively viewed pronounceable nonwords. These stimuli contain both consonants and vowels arranged in such a manner that they can be pronounced but do not form a known word in English. In this instance we have a stimulus that combines all of the features of false fonts and consonant letter strings as well as following the pronounciation rules of the English language. An example of a typical stimulus is shown above the image.

Finally, in D subjects passively viewed words. These stimuli obviously combine all of the features of the other stimuli and, in addition, they convey meaning. An example of a typical stimulus is shown above the image.

Inspection of these four images reveals that pronounceable nonwords and words cause much more marked responses in the visual areas of the brain than do the false fonts and consonant letter strings. The conclusion to be drawn is that in an English speaker the normal brain has learned to recognize, in an almost automatic fashion, symbols that behave according to the rules of the English language. Thus, the response defines a region in the normal brain concerned with the analysis of visual word form. It is of interest that occasional patients who have suffered stroke in this part of the brain cannot recognize groups of letters as words even though they can identify the individual letters.

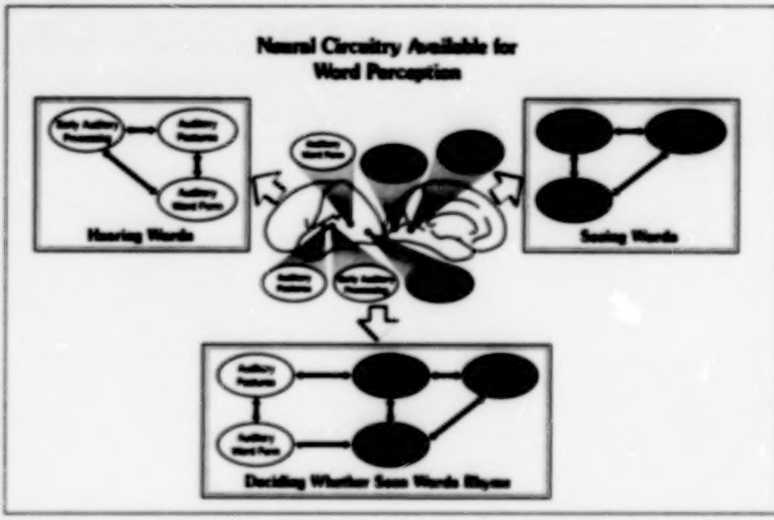


Figure 5. Neural circuitry available for word perception. *On the left* are the outer and *on the right* the inner surfaces of the left brain upon which are schematically located (in a very general way) areas of the cerebral cortex concerned with processing of auditory (heard) and visual (seen) words. Although the scheme depicted in this figure greatly oversimplifies the functional anatomy involved, it is intended to convey the modular nature of the process. Viewed in terms of brain organization, the process can first be divided into the perception of heard words (open ellipses to the left) and seen words (closed ellipses to the right). Within these two domains the process is further subdivided into its component parts. For example, a seen word is processed in multiple regions of the cortex representing local ensembles of nerve cells regionally specialized for organizing and sorting incoming visual information (early visual processing) for distribution to specialized processing areas of the visual system concerned with such things as lines and their orientation, color, and motion (visual features). These areas of the brain can be activated by a variety of stimuli including words. When confronted with a word these areas are stimulated in concert with additional areas concerned with the recognition of properties unique to words (visual word form). This temporarily creates a distributed network of specialized neuronal ensembles (much as we might set up a conference telephone call) designed to facilitate visual word perception *(upper right)*. A similar process appears to take place for heard words but in anatomically separate areas *(upper left)*.

The flexibility of these functional relationships is likely to emerge as an important feature of brain organization. This is nicely illustrated by increasing the complexity of the task. For example *(below)*, visual areas as well as selected auditory areas are recruited to make a judgment about whether pairs of seen words rhyme. Obviously in such a task an internal auditory analysis of a pair of seen words is required and, not surprisingly, an appropriate brain circuitry is recruited for the task.

standard neurologic examination. However, the subject was unable to perform this simple verb-generating task, producing significantly more errors than normal controls and showing no evidence of improvement with practice. Our results combine to suggest the cerebellum plays a significant role in response evaluation even in high-level information-processing tasks.

Our experience with this case of right cerebellar stroke illustrates a very important benefit to an understanding of the normal function of the human brain obtained, in this case, with modern imaging techniques. Armed with the new knowledge that the cerebellum is involved in a high-level information-processing task devoid of any motoric components, we were prompted to ask entirely new questions of our patient. This observation revealed a deficit, the nature of which was unappreciated by the patient, his family, or his physicians. Insights like this can only help in better understanding our patients and planning their rehabilitation.

Finally, one additional preliminary observation may be of importance in understanding the information-processing role of the responses observed in the task of speaking an appropriate verb for a seen or heard noun. Specifically, the responses in the left prefrontal cortex, the left temporal cortex, the anterior cingulate cortex, and the right cerebellar hemisphere were only present when subjects were first exposed to this task (i.e., when the task was novel and required active attention). Practice of the task (i.e., generating verbs to a specific list of nouns) resulted in the disappearance of the left frontal, left temporal, anterior cingulate, and right cerebellar hemisphere responses. When this skill had been mastered, the areas of brain activated could not be distinguished from those used in simply repeating seen or heard nouns (a very automatic task for skilled readers). These results suggest a role for certain areas of the brain in the acquisition of a new skill, in this case linguistic, but not in the performance once it has been learned. These observations provide our first glimpse of brain mechanisms that may underlie the automaticity of many familiar routines such as driving a familiar road to work. Such acts are done often without much conscious effort. Certainly the reorganization of brain functional anatomy as we learn reflects a remarkably flexible use of brain resources that results in great efficiency in the allocation of a finite capacity.

What do the results of our studies of single-word processing suggest about the modular organization of the human brain? They suggest a modular organization consisting of multiple, widely distributed ensembles of neurons. Each of these modules can perform highly specialized processing, most of which have yet to be fully defined, that can be assigned where needed to a variety of tasks. One might imagine, as task demands dictate, that appropriately selected modules are temporarily "connected" (much as we might connect several individuals in a conference telephone call) to accomplish specific tasks. Highly localized areas of the brain for observable behavior, as orginally postulated by the devotees of

phrenology (i.e., regions devoted to mathematical reasoning, love, etc.), have no meaning in such a formulation. Rather, behavior is the product of spatially distributed modules linked, temporarily, in time for the achievement of a specific behavior.

Conclusions

Changes in neuronal activity are accompanied by rapid (<1sec) changes in local blood flow and metabolism in the brain. Positron emission tomography (PET), a modern, nuclear-medicine, brain-imaging technique, accurately and rapidly (<1min) measures changes in local blood flow. Assuming all mental activity is accompanied by changes in local blood flow, PET is ideally suited to accomplish the task of relating changes in local neuronal activity to mental activity.

Using PET measurements of local blood flow and strategies for accurately localizing these changes in the normal human brain, the general topography of systems concerned with the analysis of words has been presented. These data demonstrate that a combination of cognitive and neurobiological approaches to the study of normal human subjects, aided by modern imaging techniques such as PET, can give us important new information about the flexible, distributed, modular organization of cognition and emotion in the human brain. Progress in our evolving understanding of the implementation of mental activities in the human brain will be dependent upon an appreciation of the distributed nature of the processing. Inferences drawn about the role of specific local neuronal ensembles in particular mental activities, heretofore inferred from the loss of function due to discrete lesions in humans, must now be guided by the knowledge that a region of the brain may be only a part of a very distributed network in which local areas contribute highly specialized component functions. As this type of information accumulates on the normal functional anatomy of the human brain, we are likely to ask entirely new questions of our patients with neurological disease. For example, it was only as a result of our studies of normal language organization that the patient mentioned earlier in this review with the injury to the right cerebellar hemisphere was evaluated for cognitive impairment and found to have a highly specific and profound deficit. We expect such examples to multiply rapidly in the future.

Positron emission tomography is not the only imaging technique likely to have an important impact on our understanding of the functional organization of the human brain (figure 1). Magnetic resonance imaging (MRI) has provided superb, gross anatomical

images of the living brain and has been used with great success in delineating the anatomy of lesions in relation to specific behavioral deficits. Recently it has been possible also to detect blood flow changes in the human brain with MRI. This exciting development suggests an even more refined look at the workings of the normal human brain. Neither PET nor MRI is likely to provide insight into the temporal relationships among the several modules subserving a specific mental operation. Electrical measurements of brain activity from surface electrodes in the form of the electroencephalogram (EEG) or event- related potentials or electrically-generated magnetic fields (magnetoencephalography or MEG) provide excellent temporal information but variably suffer from a difficulty in localizing the source of the electrical signal. In the future one envisions an interaction between PET/MRI and EEG/ERP/MEG in which the former techniques will provide an accurate anatomical description of the functional anatomy of a system of modules underlying a particular mental operation and the latter techniques, guided by this information, will provide us with a description of the temporal relationships among the constituent modules. The prospects that new information will arise about the functional organization of the human brain from the *combined* use of these new imaging methods along with other investigative techniques in the neurosciences are quite exciting. I think one can be hopeful that the insights gained from such work will provide a more rational basis for the understanding and treatment of some of humankind's most devastating diseases.

Suggested Readings

Petersen, S.E., P.T. Fox, M.I. Posner, M.A. Mintun, and M.E. Raichle. 1988. Positron emission tomographic studies of the cortical anatomy of single word processing. *Nature* 331:585–89.

Petersen, S.E., P.T. Fox, A.Z. Snyder, and M.E. Raichle. 1990. Activation of extrastriate and frontal cortical areas by visual words and word-like stimuli. *Science* 249:1041–44.

Posner, M.I., S.E. Petersen, P.T. Fox, and M.E. Raichle. 1988. Localization of cognitive functions in the human brain. *Science* 240:1627–31.

Posner, M.I., and M.E. Raichle. 1994. *Images of Mind*. Scientific American Library. New York: W.H. Freeman and Co.

Raichle, M.E. 1987. Circulatory and metabolic correlates of brain function in normal humans. In *Handbook of physiology*: ed. V.B. Mountcastle and F. Plum. *The nervous system* 5:643–74. Bethesda, Md.: American Physiological Society.

Raichle, M.E. 1994. Visualizing the mind. *Scientific American*, April: 58–64.

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SOME RELATIONS BETWEEN MIND AND BRAIN

John R. Searle

In spite of important recent advances in our understanding of the brain, we still remain largely ignorant of many of the most important features of human neurophysiology. We do not yet know exactly *which* processes in the brain produce consciousness, nor *how* exactly the sequence of conscious states is produced. We do not know the mechanisms binding all of the disparate stimuli into unified states of conscious awareness. We do not even know for sure how memories are stored in the brain. We do not know how children learn to speak languages; and we have virtually no account of human creativity.

I believe that our ignorance of the brain, together with certain philosophical mistakes we have been making for centuries, have produced a whole series of harmful confusions. My aim in this article is to remove some of these. The first confusion, which has recently become pervasive, is the idea that the brain is a hardware computer mechanism, and that what we call "the mind" is the computer program or software. As the literature on cognitive science often says, "The mind is to the brain as the program is to the hardware" (Johnson-Laird 1988). In order to distinguish this view from other and more modest versions of artificial intelligence, I have baptized it "Strong Artificial Intelligence" or "Strong AI" for short. Unlike many other confusions in this field, Strong AI has two important advantages: First, it can be stated quite clearly, and second, it can be refuted swiftly. The refutation will not take more than a few paragraphs.

The easiest way to test any theory of the mind is to try out on one's self. If the mind is a computer program, then one could acquire any cognitive capacity simply by implementing the program for simulating that cognitive capacity. One could, for example, understand Chinese by implementing a Chinese-understanding

program. Well, let us try it. Suppose I am locked in a room with several bushel baskets full of Chinese symbols. Suppose, as is indeed the case, that I do not speak a word of Chinese. Imagine further that I have the rule book that enables me to match Chinese symbols with other Chinese symbols, and enables me to hand back Chinese symbols to people outside the room in response to symbols they give me into the room. Let us also suppose, unknown to me, the people outside the room know what these Chinese symbols mean, and that they have written the rule book in such a way that the input symbols, which they think of as questions, will receive the right output symbols from me, which they think of as answers. In short, we imagine that the people outside the room think of the rule book as a computer program for manipulating the symbols; they think of the bunches of symbols I have inside the room as a data base; they think of the input symbols as questions; they think of the output symbols as answers; and me, they think of as the computer. We could suppose that after a while they get so good at writing programs, and I get so good at shuffling the symbols, that my answers are indistinguishable from those of a native Chinese speaker. All the same, however, I do not understand a word of Chinese, and given the way we have structured this little experiment, there is no way I could learn Chinese just by manipulating the Chinese symbols. All I have is a set of symbols, a rulebook for manipulating them, and a set of procedures for giving out output symbols in response to input symbols.

Now, and this is the point of the parable, *if I do not understand Chinese solely on the basis of implementing a Chinese-language-understanding program, then neither does any other digital computer, solely on that basis, because no other digital computer has anything that I do not have.* The power of the digital computer derives from the fact that its procedures are purely formal; that is to say, they are defined entirely in terms of the manipulation of symbols, where the symbols are specified entirely in terms of abstract features, such as shape or voltage level. The symbols are identified purely by virtue of their formal features, and the rules for their manipulation make reference only to these formal features, rather than to their meaning or interpretation. In short, computer programs are defined syntactically; and the Chinese Room Argument rests on the obvious principle that syntax by itself is insufficient to determine semantics. Just having rules for manipulating the formal symbols is not enough to give any meaning or interpretation to those symbols.

For those who like to see the logical structure of arguments laid out, this one has a very simple structure:

1. First premise: Programs are formal or syntactical. (This is part of the definition of a program.)

2. Second premise: Minds have contents or semantics. (This is just an empirical fact about human minds. Minds have more than meaningless symbols. The symbols typically have a content or semantics.)

3. Third premise: Syntax by itself is not identical to semantics, nor is it sufficient for semantics. (This follows from the standard definitions of syntax and semantics, but in any case, the Chinese Room example serves to remind us of this logical truth.)

From these three follows the conclusion.

4. Conclusion: Programs are neither by themselves the same as—nor are they sufficient for—minds. (And this is just another way of saying: Strong AI is false.)

You can see the force of the Chinese Room Argument if you contrast me in the Chinese room manipulating Chinese symbols with me answering questions in English. We might suppose the people outside the room also give me questions in English, and I write back answers to questions in English. We then have a situation where my answers to the questions in English are indistinguishable from those of a native English speaker, because I am a native English speaker; my answers to the questions in Chinese are indistinguishable from those of a native Chinese speaker because I have been programmed to answer questions in Chinese. From the outside, I look equally proficient in both Chinese and English. But from the inside, there is an enormous difference: I understand English perfectly, but I do not understand Chinese at all. Where Chinese is concerned, I am just a digital computer.

I first presented the Chinese Room argument over ten years ago. I think the argument is quite decisive, though it has been attacked from a number of quarters. Indeed, there must be at least a hundred published attempts to refute it. I believe I have by now seen most of the possible variations on attempts to attack it, but none of them seems to me to have any force whatever. Of course, when I say that, I have to recognize that any view is subject to subsequent revision, and perhaps someday someone will come along with a convincing counterargument, but so far I have not seen any such argument.

However, though the Chinese Room Argument is decisive against Strong AI, there is a slightly weaker version of the computa-

tional theory of the mind which is immune to this argument. Just to have another name, I will call this weaker version "Cognitivism," because it is a view commonly held in cognitive science. Here is how it goes.

Perhaps there is more to the brain than there is to the computer, perhaps there is more to the mind than there is to the computer program, but all the same, it might be the case that the brain is *at least* a digital computer, and the mind is *at least* a computer program. There might be something in addition to syntactical processes going on in the brain, but perhaps an essential part of any mental state is its computational structure. And perhaps mental processes are all computational processes, operating over the computational structure of these mental states. In short, even if the program is not *sufficient* for the mind, perhaps it is *necessary* and *essential* for the mind. If so, we could still study the mind without having to know anything about the brain, we could still study the mind simply by doing computational simulations of its processes.

Cognitivism, as stated, is not refuted by the Chinese Room Argument. But I believe it can also be refuted swiftly, though the argument is somewhat more subtle. To refute it, we have to state a little more precisely what a computer is and what a program is. On the standard definition of a computer and computer program, a computer is a device that can perform four and only four operations. It can erase a 1 and print a 0. It can erase a 0 and print a 1. It can move one square to the left. It can move one square to the right. That is all it does. It has a set of instructions for performing these operations, and that set of instructions is called the program. The instructions in the program are always of the form, "Under condition C, perform act A." That is, "if C, then A."

Now, I am a very literal-minded person, and my natural inclination when I hear such a definition is to think that I can open up my computer and look for a tape that contains 0's and 1's and a device for printing and erasing. But of course, if you open your home computer, you are very unlikely to find any 0's and 1's or even a tape. We are told, however, by the experts, that this does not really matter, because anything that can *function* as a 0 or a 1 and anything that can function as if it were a tape on which 0's and 1's were being printed is quite sufficient. So, for example, different voltage levels might correspond to 0's and 1's. So far, so good. But now the next question arises, what exactly are we supposed to look for in the brain? We are told that the brain is a digital computer and its operations are computational operations. What physical features of the brain are supposed to correspond to these

claims? This is a more difficult question than might at first seem to be the case.

In order to probe this question, we need to make a distinction between those features of the world that are, so to speak, intrinsic and those that are defined relative to observers. The natural sciences study intrinsic features of the world, features such as gravitational attraction, electromagnetism, or mass. But not all features of the world are in that way intrinsic; some are defined relative to observers, users, and human agents generally. Thus, for example, something is money only if people use it as money. There is no natural science of money in a way that there is a natural science of matter, because although all money is matter in some form or other, whether or not a given piece of matter is money depends not on its intrinsic physical features but on the use, attitudes, stance, and so forth that people take toward the piece of matter. There are, for example, no chemical or physical properties of the bit of paper in my wallet that are sufficient to determine that it is money. It is money only relative to users or observers.

I propose then to distinguish between two kinds of features of the world: intrinsic features, which are studied by natural science, and observer-relative features, many of which are studied by the social sciences. The problem with cognitivism, as I have stated it, is that syntax, and hence computer programs, are not intrinsic features of physical systems—they are always observer-relative. Some physical feature is a 0 or a 1 only relative to some agent who assigns a syntactical interpretation to that feature. But no physical features intrinsically determine a computational interpretation. It follows from this fact that we could not discover that brains were digital computers, because something is a digital computer only relative to some agent who uses it as a computer, who programs it as a computer, or who assigns a computational interpretation to its processes.

So the mistake behind cognitivism is a very deep one. Cognitivism supposes we could discover as a matter of fact that the brain is a digital computer and that the mind is a set of computational processes implemented in the hardware of the brain. But, as stated, this thesis turns out to be meaningless. If the thesis is that the brain is intrinsically a digital computer, then the answer is: Nothing is intrinsically a digital computer. Something is a digital computer only relative to some agent who uses it or treats it as a digital computer. If the thesis is that the brain could be used as a digital computer, then the answer is: Anything can be used as a digital computer. Anything, any process whatever, can have a computational inter-

pretation assigned to it. This is a different argument from the Chinese Room Argument. Just as the Chinese Room Argument showed that semantics is not intrinsic to syntax, this argument shows that syntax is not intrinsic to physics.

So far then, I have devoted my efforts to refuting two mistaken conceptions of the brain. One is that the brain is just a computer and that mental processes are just computational processes. The second is that the brain is at least a computer and that the essential mental operations in the brain are computational operations. But assuming we have refuted these views, we are still left with a question, indeed a challenge. What exactly is the relation of the mind to the brain? The computational theories we have considered have answers to that question. If we are going to reject those answers, we need an answer of our own. What is it?

You will recognize that this question is the traditional "mind-body problem." I think the mind-body problem has a rather swift and easy solution, but we have been blocked from seeing this solution by a combination of scientific ignorance (we do not know how the brain works) and philosophical confusion (we are still accepting a series of conceptual distinctions that go back to Descartes in the seventeenth century; indeed, they go back two thousand years). The basic philosophical mistake we have been making is to assume that two, and only two, kinds of phenomena exist in the world, mental and physical, and that something cannot be both mental qua mental and physical qua physical. I now want to challenge these assumptions.

If we ask ourselves, in light of our current knowledge of the brain, limited though it is, what exactly are the relations between the mind and the brain, it seems to me the answer to that question is rather easy. We know in fact that *mental states are caused by neurophysiological processes in the brain.* We do not know all of the details of how they are caused, but we have a general idea about how the sequence of events that begins at the stimulus of peripheral nerve endings, and continues right through into the deepest portions of the brain, eventually causes conscious states, such as pains, tickles, itches, thoughts, and feelings. Even though we are ignorant of the details, we have enough information about the brain to know that all mental phenomena are caused by neurophysiological processes in the brain.

But that leaves us with a residual question: Granted that mental processes are caused by brain processes, what exactly are these mental events? How do they fit into our overall ontology? Granted that my pains, tickles, itches, thoughts, and so on are all

caused by sequences of nerve firings, the question remaining is: What is their nature as mental events? How can we fit them into our theory of the world?

Once again, it seems to me the answer to that question is not too difficult. To the first proposition that mental states are caused by neurophysiological processes in the brain, we need to add a second: ***Mental states are simply higher-level features of the brain.*** My present state of consciousness is a higher-level feature of the brain in the same sense, for example, that the solidity of the table or the liquidity of the water in this glass is a higher-level feature of the table or the glass of water. By "higher-level" I mean it is a feature of the entire system, but not a feature of the microcomponents of which the system is composed. So the whole glass of water is in a liquid state, but an individual water molecule is not in a liquid state. Similarly, the system of neurons is conscious, but it is not the case that each individual neuron is conscious.

But one might ask, how can both these relations hold? How can it both be the case that mental processes are caused by brain processes, and yet mental processes are just higher-level features of brains? How can there be a causal relation and an identity relation between the same pairs of phenomena? Well, in fact such relationships are quite common in nature. Consider the examples I just gave: the water in this glass is liquid. The liquidity is causally accounted for by the behavior of the microelements, by the behavior of the molecules. Alter the behavior of the molecules and you will produce solidity; if, for example, you slow down the movement of the molecules sufficiently, the system becomes solid ice. But the liquidity, which is caused by the behavior of the molecules, is not a separate stuff, it is not a separate substance. It is not something that, so to speak, oozes out of the system of molecules. The liquidity is a feature of the system. It is a state that the system is in. Thus, we have a simple model of how a system can at the same time be composed of microelements, and yet the behavior of those microelements causes higher-level features of the very system that is composed of those microelements.

This, I am suggesting, is the right model for thinking of the relationship between consciousness and the brain. (Of course, there are many disanalogies between liquidity and consciousness. I am only using this as a simple example to show how the same feature can stand in causal relations to the elements of a system and at the same time be a feature of the system that is composed of those elements.) The system of microelements behaves in such a way as to cause a higher-level feature, but the feature is not a feature of any

particular element. I cannot say of any neuron, "This one is thinking about my grandmother," any more than I can say of any molecule of water, "This one is liquid" or "This one is dry." Liquidity, wetness, dryness exist at a much higher level than that of the individual molecule. Consciousness, memory, and so on are similar. These are features of a system that is made up of the microelements—neurons, synapses, and so forth—and the behavior of the microelements causes these higher-level features of the system.

To summarize the discussion so far, I have made two claims. The first is that the computational model of mind/brain relationships is inadequate to account for the actual relations between mental and neurophysiological phenomena. The second is that the traditional mind-body problem has a rather swift solution, once we recognize that there is no reason to accept the traditional claim that mental implies nonphysical and physical implies nonmental. The solution is that mental phenomena are caused by lower-level neurobiological processes in the brain, and the mental phenomena themselves are higher-level features of the brain.

To conclude, I would like to draw some of the policy implications of the claims I have been making. I believe that if we had an adequate account of mind/brain relationships, and a correct understanding of the possible contributions of artificial intelligence to the study of mind/brain relationships, we would save the federal government from making a lot of mistakes, and incidentally, from wasting a lot of money.

Traditionally, we have believed there is a separate category of "mental illnesses." That is, we have believed, there are really two types of illness, physical illness and mental illness. I believe this is a profound mistake. There are illnesses of the body, and in one way or another, all illnesses involve a malfunction of our physical system. Typical brain-based illnesses are clinical depression and schizophrenia. It is a tragic mistake to suppose these exist independently of the physiology of the patient. In my childhood generation, parents with schizophrenic children were made to feel terribly guilty, were made to feel that somehow they were at fault, because the child suffered from these terrible schizophrenic symptoms. Similarly, the patient who suffers from clinical depression often feels, somehow or other, it is his fault, that somehow or other, his depressed state is the result of some thought processes for which he is responsible. As we come to understand these illnesses better, we have come to see that they have a physiological basis.

What I am suggesting, in short, is that no ontological category of "mental illness" as opposed to physical illness, exists. There are indeed forms of mental disorders. Most of these involve either acute misery to the patient or an inability on the part of the patient to function in society. Without exception, these are all based on some form of malfunctioning of the neurophysiology. But there are not, in addition, a set of illnesses involving a separate ontological category of "the mind."

Finally, I turn to artificial intelligence. As far as the study of the brain is concerned, we have often been in the position of the drunk who, having lost his car keys in the bushes, looks for them under the street light, because the light is better there. Rather than studying the brain, which is a hard subject to study, we have tended to suppose that we could avoid having to do the hard work of brain research by building computational models of cognitive processes instead. Now, in their own area, I find these computational models quite useful, but it is best to think of them as aids to studying the brain. Computational models of brain functioning are useful in the way computational models of digestive functioning or molecular behavior are useful. But it is a mistake to suppose the computational simulation is a substitute for actual studies of brain functioning.

I believe that much—though not all—research in artificial intelligence was based on false premises. To put the point brutally, my impression is that much AI funding in the United States has been based on lying to Congress over a period of many years. The two forms that the misinformation takes are: first, the claim that what is being done is essential for national defense, and second, that computer programmers are creating minds by sitting at their terminals and typing out programs in Lisp and Fortran. I am not professionally qualified to assess the defense-based claims, but I have been assured by several people competent in AI that many of these claims are false. But about the latter point, that by creating a computer program we are creating a mind, I can demonstrate that view to be mistaken. Since the program is defined purely formally or syntactically, and since the formal syntax is never by itself sufficient for cognitive processes, it follows that programs are not minds.

So, my conclusion is this: If we are really to understand the mind, we need a much better understanding of brain processes. I hope the decade of the brain will provide some of the great breakthroughs we have all been waiting for in understanding the operations of the human brain.

Suggested Readings

Johnson-Laird, Philip. 1988. *The computer and the mind : An introduction to cognitive science*. Cambridge, Mass.: Harvard University Press.

Searle, John R. 1980. Minds, brains, and programs. *The behavioral and brain sciences*, 3:417–57.

Searle, John R. 1984. *Minds, brains and science*. Cambridge, Mass.: Harvard University Press.

Searle, John R. 1990. Is the brain's mind a computer program? *Scientific American* 262, no. 1 (January): 26–31.

Searle, John R. 1990. Is the brain a digital computer? Presidential Address to the American Philosophical Association. *Proceedings of the American Philosophical Association*.

Searle, John R. 1992. *The rediscovery of the mind*. Cambridge, Mass.: MIT Press.

Learning and Memory

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THE CELLULAR BASIS FOR LEARNING AND MEMORY

Charles F. Stevens

How does the brain store memories about people, places, and things? I shall present an answer to this question in a brief overview that summarizes our current understanding of the cellular basis for learning and memory. Stated briefly, learning appears to occur through the strengthening of connections between nerve cells in the brain; this strengthening comes about when these connections are used together and repeatedly.

Understanding more precisely how the connections become strengthened requires a description of brain cell structure and how cells within the brain communicate with one another. The cells responsible for the brain's operation are called nerve cells or neurons. These neurons are so small and densely packed that a bit of brain the volume of a grain of rice contains about a million nerve cells.

The Basic Nerve Cell

Three distinct parts of a neuron can be recognized (figure 1). The central part or cell body contains the cell's genetic information and machinery for protein synthesis. The second part is a set of fine-branched tubelike protrusions from the cell body called dendrites. Because a neuron's dendrites often are arrayed in a tree shape, they are described as the neuron's dendritic tree. The third part of the neuron is another tubelike protrusion from the cell body called the axon. This fine thread, about one-hundredth the diameter of a human hair, transmits information from one part of the brain to another or between the brain to parts of the body (like muscles). Axons that hold the length record are those in the giraffe's vagus nerve; they run about fourteen feet from the base of the brain through the neck down to the stomach. The longest human axons are about a yard long. A piece of brain the size of a

rice grain contains, in addition to a million neurons, about twenty miles of axons.

How do nerve cells communicate with one another? Information flows into the neuron primarily at the dendrites, and all of the information received over the neuron's dendritic tree is combined in its cell body. If the total incoming signal is large enough, the neuron generates nerve impulses that travel down the axon to an area of cell membrane specialized for contact and communication with other nerve cells, as will be described in more detail below.

Nerve cells in the brain are arranged in circuits that underlie brain function. Each neuron receives signals from about ten thousand other neurons, and each neuron in turn sends signals to about ten thousand target neurons. These connections are not random but rather make a very specific pattern. If we identify by letters cells of different shapes, biochemistries, and locations, the cells of type A would always make connections to cells of type B. Cells of type B would always make connections to cells of type C, and so on. Hundreds or thousands of letters would be required to describe the circuits accurately.

The site of contact for information flow between two neurons—usually between the axon of one neuron and the dendrite of another—is called the synapse. How many synapses are there in a human brain? One answer is that a rice-grain-sized bit of brain contains (in addition to a million neurons and twenty miles of axons) about ten billion synapses. Another way to answer is to have someone pay a penny for each of the synapses in your congressional representative's brain; you would have about three trillion dollars, which is just about enough to pay off the entire national debt. A penny for a synapse is actually quite a bargain because, as you shall see, the synapse is an incredibly complicated machine and is associated with the storage of memories.

The Working of a Synapse

The mechanism by which synapses operate is as improbable as it is complicated. Like beads on a string, axons have special structures called axon terminals that are specialized for sending signals. The axon terminal contains many microscopic bags, called synaptic vesicles (figure 1), each of which is filled with one of a variety of chemicals known as neurotransmitters. As a nerve impulse sweeps along the axon and reaches each terminal, the synaptic vesicles fuse with the terminal's outer membrane, releasing the neurotransmitter into the fluid that fills the narrow space between the information sending (or presynaptic) neuron and the information

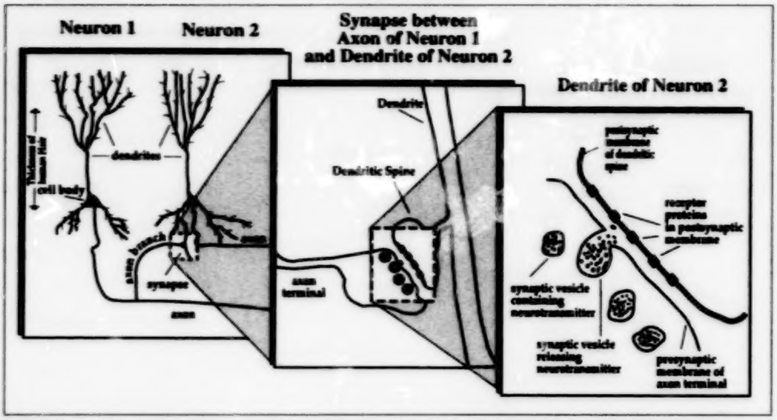

Figure 1. The basic nerve cell and the mechanism of a synapse. The neuron has three distinct parts: the cell body, the dentrites, and the axon.

receiving (or postsynaptic) neuron. Note that the synapse is a one-way communication link because only the sending neuron contains the synaptic vesicles.

The dendrite of the postsynaptic neuron has specializations for receiving signals. Its surface has small protrusions—something like thorns on a rose—called dendritic spines. These structures, each about a millionth of a yard long, were discovered a hundred years ago by the great neuroanatomist Santiago Ramón y Cajal. Special proteins called receptors are embedded in the outer membranes of the spines. When the neurotransmitter released by the axon diffuses to the dendrite's membrane, some of it binds to these receptors and causes them to change their shape. That shape change of the receptor protein initiates a cascade of events in the postsynaptic cell, the consequence of which is the generation of an electrical signal in the receiving neuron. A synapse can send signals dozens of times per second. So you see, a penny is a bargain price for a synapse (and we have not described the synapse's most interesting properties yet).

Most of the drugs and poisons—legal and illegal—that act on the nervous system work at synapses. Much research has been done to determine in detail how these drugs work. Some drugs affect the presynaptic mechanisms, that is, the release of neurotransmitters; others modify the postsynaptic action of neurotransmitters. For example, drugs such as the caffeine in a cup of coffee can increase the amount of neurotransmitter released by a presynaptic nerve impulse. Other drugs can mimic or block the natural neurotransmitters

at synapses. The street drug known as "angel dust" (phencyclidine) is thought to act by blocking the effect of a neurotransmitter at certain types of receptors. Valium increases the effectiveness of the neurotransmitters that act on another special kind of receptor.

Storing Memories

Now we turn to some of the details of how memories are stored. When a synapse is active in just the right way (an example of "the right way" is given later), the signal sent from the presynaptic cell to the postsynaptic cell becomes more effective in producing nerve impulses: the synapse becomes stronger.

Scientists are exploring a number of different ways that synapses can become more effective. One example of synapse strengthening is called long-term potentiation, because the synapses are made more potent and the effect lasts for weeks. Long-term potentiation does not strengthen all the synapses of a neuron but only the particular ones that have been used simultaneously and repeatedly. Note that many of a neuron's synapses are inactive much of the time.

A complicated sequence of events underlies long-term potentiation. These events occur at synapses where the neurotransmitter is usually the amino acid (one of the building blocks of proteins) glutamate. The postsynaptic membrane, part of a dendritic spine, has two distinct types of receptors that bind glutamate. This may seem like a lot of detail but these receptor types have important functional differences that are crucial to the learning mechanism.

The pharmacologists who first studied the synaptic receptors we are talking about were looking for drugs that would mimic glutamate. One of these drugs that chemists made to have a structure similar to glutamate is called N-methyl-D-aspartate (NMDA). But this man-made chemical turns out to substitute for glutamate at only one of the two types of receptors. Therefore, this receptor type is designated the NMDA class or more briefly, the NMDA receptor (even though it actually receives glutamate in the brain). The psychological effects of angel dust are thought to result from the blocking of glutamate action at these receptors. The other glutamate receptors are unaffected by NMDA, so they are called non-NMDA receptors.

The sequence of events leading to long-term potentiation has been unraveled by neuroscientists over the past five years or so. A nerve impulse comes down an axon to the axon terminal, and glutamate is released there when glutamate-containing vesicles fuse with the presynaptic membrane. The released glutamate dif-

fuses across to the postsynaptic membrane, where it binds to both NMDA and non-NMDA receptors. The binding to non-NMDA receptors initiates a signal in the postsynaptic cell which, as I have previously mentioned, is integrated with signals from all the other synapses to determine whether that neuron will generate nerve impulses. But the NMDA receptor is playing a different role because it has two requirements for functioning: It must bind glutamate (as do the non-NMDA receptors), and it must also determine that at least a certain number of other synapses—no matter which ones—on the neuron are active. (The interesting mechanism by which the NMDA receptor detects whether or not other synapses are active is well understood, but I will not describe it here.)

When these two requirements are met, the NMDA receptor opens a pore in the membrane. Calcium ions, which are maintained (by the expenditure of metabolic energy) at higher concentration outside the cell than inside it, flow into the dendritic spine. This inflow of calcium is key. The calcium activates enzymes in the dendritic spine to make a special chemical that carries a message back to the presynaptic cell. By a series of biochemical events that neuroscientists have only partly determined, the synapse then is made stronger. Thereafter, for a long time, each nerve impulse arriving at the axon terminal releases more neurotransmitter than did impulses that arrived before the synapse was strengthened. When some synapses are strengthened, their influence supersedes that of other, unstrengthened synapses and they take on a larger role in the postsynaptic neuron's decision of whether to fire nerve impulses. Whereas before the strengthening several active synapses were needed to send a sufficiently large signal into the postsynaptic neuron, after strengthening the synapse can by itself send a large signal.

This complex mechanism underlies the changes in a particular brain region called the hippocampus that are responsible for storing memory. (This brain area is called the hippocampus because it is shaped something like a seahorse: hippocampus is Latin for seahorse.) Let me give an example of the type of animal experiment that supports the connection between this synaptic strengthening and learning. Consider complex spatial learning in rats. Researchers know how to determine how well a rat can remember a map of its environment. Certain drugs can keep the NMDA receptors from operating, and, when given to rats, these drugs—by blocking the function of NMDA receptors and thereby preventing synapse strengthening—prevent the animals from learning a map of their environment. So blocking strengthening also blocks learning.

To summarize: connections between nerve cells release a neurotransmitter. In the hippocampal neurons involved in memory formation, the neurotransmitter binds to two kinds of receptors, one of which participates in normal signal transmission. The other receptor type detects the coincidence of activity between this synapse and other synapses on the same cell. If there is a conjunction of activity, these receptors open pores so that calcium enters the postsynaptic neuron. The calcium triggers a cascade of events that send a signal back to the presynaptic cell, which increases the quantity of neurotransmitter released when subsequent nerve impulses arrive at the synapses—the synapse has been strengthened.

Critical Periods for Synaptic Plasticity

Our understanding of cellular mechanisms for learning and memory have implications both for the beginning of a person's life and for the ending. The number and distribution of synapses change especially during infancy and childhood.

The mechanisms I have described can strengthen synapses in the hippocampus for a few weeks. One of the most important findings of modern neurobiology is the following: Certain synapses that are strengthened transiently during defined periods of life become permanent for the remainder of the person's life, whereas other synapses that do not get strengthened are actually eliminated forever from their neurons. Therefore, experience during development directs a structural and functional reorganization of the brain.

The person's age at which strengthened synapses are retained and others are removed in a particular part of the brain is called the critical period for that brain region. After the critical period, additional changes cannot occur. This observation has important ramifications for human development. For example, the brain area that processes visual input has a critical period. If a child has a vision defect—for example, crossed eyes that is not corrected in the first few years of life—the visual regions of the brain do not develop correctly. Later, even if the eye problem is corrected, the child's vision remains blurred. As another example, the critical period for language areas of the brain ends about puberty. An adult just cannot learn to speak a new foreign language without an accent once the language area critical period has passed.

At the end of a critical period, activity-dependent synapse changes can no longer occur. These changes require the NMDA receptor: in animal experiments, when the NMDA receptors have

been blocked with drugs, the functional and structural reorganizations of the brain in development also are blocked.

The implication for social policy is that children need certain experiences for their brains to develop correctly, and these experiences cannot be long delayed. Once a critical period has passed, the child has in effect a different brain, and there is no getting back the earlier flexibility. Different regions of the brain have different windows of opportunity, and after those periods they cannot be changed further.

Stroke Damage

The structures involved in learning and memory also are influenced by potentially catastrophic events that occur later in life. One example is a stroke, the third most common cause of death in the United States. The most usual type of stroke is like a heart attack of the brain: an obstruction of the blood supply deprives brain cells of the oxygen they need to survive. But the damage resulting in a stroke involves more than just the loss of cells deprived of oxygen. While these cells cannot be saved, neurons in a surrounding area die owing to a cascade of reactions involving the NMDA receptors.

As the neurons deprived of oxygen die, they release the neurotransmitter glutamate, which triggers excessive activity in the surrounding cells (synapses cannot tell that this glutamate comes from dying cells and are activated just as if many nerve impulses had arrived). As all the cells are firing nerve impulses, the NMDA receptors detect the coincident activity and open the pores that let in calcium. Entry of calcium is required for strengthening synapses in long-term potentiation, but when too much calcium enters a neuron the result is cell death. This chain of events is called excitotoxicity. In effect, it is an exaggerated form of the learning response.

Several pharmaceutical companies have investigated agents that may block excitotoxicity. Some drugs have been demonstrated effective in animal tests, and human trials are currently under way.

Conclusion

In summary, I have presented a cellular neurobiologist's view of what the hippocampus does and how it stores memories in the strengths of the synapses. The challenge for the future is to sort out the details and, most interesting, to determine how the relatively short-lived changes in long-term potentiation can be translated into memories that last a lifetime.

Suggested Readings

Dudai, Yadin. 1989. *The neurobiology of memory: concepts, findings, trends*. New York: Oxford University Press.

Hille, Bertil. 1984. *Ionic channels of excitable membranes*. Sunderland, Mass.: Sinauer Associates, Inc.

Stevens, Charles F. 1986. The neuron. In *Progress in neuroscience* ("readings from *Scientific American*"), 4–15. New York: W.H. Freeman and Co.

NEURONAL PLASTICITY AND LEARNING

Eric R. Kandel
and
Robert D. Hawkins

We are witnessing a dramatic unification within the biological sciences. The ability to sequence genes, and to infer the amino acid sequence of the proteins they encode, has revealed unanticipated relationships between proteins encountered in different contexts. As a result, there is now a general plan for the function of cells that provides a common conceptual framework for several previously unrelated disciplines: genetics, biochemistry, immunology, development, cell biology, and neurobiology.

Independently, a less heralded but equally profound unification is occurring between neuroscience, the science of the brain, and cognitive psychology, the science of the mind. Whereas the unification within the biological sciences has occurred rapidly during the last decade, the unification of neuroscience and psychology has occurred gradually over several decades. But now the pace is quickening, and the ability to study the biological basis of mental function is providing a new framework for examining perception, language, memory, and conscious awareness. A particularly fascinating example of this new framework can be seen in the study of learning, where elementary aspects of the neuronal mechanisms important for several behaviorally different types of memory storage are being studied on the molecular level. As a result, the analysis of learning may provide the first molecular biological insights into a mental process and thereby extend the scope of unification by bridging cognitive psychology and molecular biology.

Learning is the process by which we acquire new knowledge, and memory is the process by which we retain that knowledge over time. Most of what we know about the world and its civilizations we have learned. As a result, learning and memory are central to our sense of individuality. Indeed, learning goes beyond the individual to the transmission of culture from generation to gen-

eration. Learning is a major vehicle for behavioral adaptation and a powerful force for social progress. Conversely, loss of memory leads to loss of contact with one's immediate self, one's life history, and one's interaction with other human beings. Thus, disorders of learning and disturbances of memory haunt the developing infant as well as the maturing adult. Down's syndrome, mental retardation, the devastation of Alzheimer's and Huntington's diseases, and the normal weakening of memory with age represent the most common of a large number of disturbances affecting memory.

The education of our young, the training of our work force, and the maintenance of the intellectual effectiveness of an aging population are central to the missions of our society. Given that effective learning and memory are central to the health of our society, what can biology contribute? In the several talks of this symposium we will outline five key insights that biology has provided. First, this research has shown that learning is not a unitary faculty of the mind but consists of at least two distinct mental processes: learning about people, places, and things (explicit learning) and learning motor skills and perceptual strategies (implicit learning). Second, these two major forms of learning are localized within the brain in different neural systems. Explicit learning importantly involves a region deep within the temporal lobe of the cerebral cortex called the hippocampus, whereas implicit learning involves the specific sensory and motor systems used during the learning process. Third, both types of learning are represented at the level of the individual nerve cells and seem to involve changes in the strength of the synaptic connections, the contact points where one nerve cell communicates with another. Fourth, for each of these two forms of learning the storage of short-term memory involves the strengthening of preexisting synaptic connections through the modification of preexisting proteins, whereas the storage of long-term memory involves the growth of new synaptic connections through the activation of gene expression and new protein synthesis. Finally, demonstration that learning is accompanied by changes in the effectiveness of neural connections and that these changes are reflected in anatomical alterations suggests a new view of the relationship between social and biological processes in the generation of behavior.

These five insights to the biology of learning have been attained only recently. Until the middle of the twentieth century most students of learning doubted that any memory function could ever be localized to a specific region of the brain. Indeed, many students of behavior even doubted whether memory was a distinct mental

function that was represented in the brain independent of attention, language, and perception.

This view of a widely distributed representation for memory contrasted sharply with the more localized view that was emerging for other mental functions such as language, perception, or voluntary movement. As early as 1861 the French neurologist Pierre Paul Broca discovered that damage restricted to the posterior portion of the frontal lobe on the left side of the brain (a region we now call Broca's area) produced a specific language deficit. Patients who suffered from damage to this area of the brain lost the ability to speak, although they could still understand language perfectly well. In 1876, the German neurologist Karl Wernicke localized a region in the posterior part of the temporal lobe where lesions caused an impairment in the comprehension of language rather than in its execution. It was only a question of time before interest would converge on memory. Is memory a discrete mental capability or is it simply ancillary to other mental processes? Is memory storage localized to a specific system of the brain? If so, are all memories stored in one place? Almost a century passed before answers to these questions came into view. During much of the period there was a continued sense that, unlike more discrete motor, perceptual, and language functions, memory could not be localized in the brain but represented a general property of the cerebral cortex as a whole.

The first person to localize successfully a particular region of the human brain concerned with memory was Wilder Penfield, a neurosurgeon at the Montreal Neurological Institute in Canada. Penfield was a student of the great British neurophysiologist Charles Sherrington, the biologist who first coined the term *synapse* for the contact point between nerve cells. At the turn of the century, Sherrington had mapped the motor representation in the cerebral cortex of anesthetized monkeys by electrical stimulation. In the 1940s, Penfield began to employ similar electrical stimulation methods to map motor, sensory, and language functions in the human cortex in patients undergoing neurosurgery for the relief of focal epilepsy. Since the brain itself does not have pain receptors, brain surgery is painless and can be carried out under local anesthesia in fully conscious patients, who can describe what they experience in response to electrical stimuli applied to different cortical areas. On hearing about these experiments Sherrington, who had always worked with monkeys and cats, told Penfield, "It must be great fun to put a question to the (experimental) preparation and have it answered!"

Penfield explored the cortical surface in over a thousand patients. Occasionally he found that electrical stimulation produced what he called an experiential response, or flashback, in which the patients described a coherent recollection of an earlier experience. These memory-like responses were invariably elicited only from the temporal lobes, never from anywhere else. Moreover, even in the temporal lobes these responses were rare, occurring in only 8 percent of all attempts at stimulation.

Although fascinating, Penfield's studies proved to be problematic. All of the patients Penfield was studying had epileptic seizure foci in the temporal lobe, and the sites most effective in eliciting experiential responses were those near these foci, so that the experiential responses might have been the result of localized seizure activity. But in 1950 more direct evidence was obtained for a role of the temporal lobes in memory. This came from the study of a few epileptic patients who had bilateral removal of the hippocampus and neighboring regions in the temporal lobe as treatment for temporal lobe epilepsy.

In the first and best-studied case, Brenda Milner of the Montreal Neurological Institute described a twenty-seven-year-old assembly line worker, whose initials were H.M. and who had suffered from untreatable temporal lobe seizures for over ten years, so that he could no longer work or lead a normal life. H.M. was operated on by the neurosurgeon William Scoville, who removed the medial portion of the temporal lobes on both sides of the brain. As a result of this removal, the seizure disturbance was much improved. But immediately after the operation H.M. experienced a devastating memory deficit—he had lost the capacity to form new long-term memories. Despite his difficulty with the formation of new memories, H.M. still retained his previously acquired long-term memory store. He remembered his name, retained a perfectly good use of language, kept his normally varied vocabulary, and his I.Q. remained in the range of bright-normal. He remembered well the events that preceded his surgery, such as the job he held, and he remembered vividly the events of his childhood. Moreover, H.M. still had a perfectly intact short-term memory. What H.M. lacked, and lacked profoundly, was the ability to translate most types of learning from short-term to long-term memory. On learning a new task he failed to retain the information for more than a minute. Asked to remember the number 584, he could repeat it immediately for many minutes. If he was distracted even briefly, however, he completely forgot the number. As a result of this difficulty in transferring information from short- to long-term memory, H.M.

did not recognize new people he met, even when he met them repeatedly. H.M. also had a profound difficulty with spatial orientation. On moving to a new house it took him a year to learn his way around it. Scoville and Milner described this deficit as "forgetting the incidents of daily life as fast as they occur." H.M. is not unique. All patients with bilateral lesions of the temporal lobe show similar memory deficits.

The Non-Unitary Nature of Memory

Originally, this memory deficit following bilateral temporal lobe lesions was thought to be global and to apply equally to all forms of new learning and long-term memory. But Brenda Milner soon discovered that this is not the case. Even though patients with temporal lobe lesions have profound deficits, they can accomplish certain types of learning tasks as well as a normal subject and retain the memory of these tasks for long periods of time. Memory is not unitary.

Milner first demonstrated this residual memory capability in H.M. by discovering that he could learn new motor skills normally. She, and subsequently Suzanne Corkin at MIT, Edith Warrington at the National Hospital in Queens Square, London, and Lawrence Weiskrantz at Oxford found that patients such as H.M. acquire and retain the memory for various elementary forms of reflexive learning, including habituation, sensitization, classical conditioning, and operant conditioning. All the learning tasks that patients with bilateral lesions of the temporal lobe are capable of remembering have two things in common: First, they all have an automatic quality. Second, their recall is not dependent on conscious awareness or cognitive processes such as comparison and evaluation. As the psychologist Lawrence Weiskrantz has remarked, these learning skills are all reflexive rather than reflective. The patient need only produce a response to a stimulus or a cue. The patient need not reflect—he need not recall or think about what is to be remembered. Thus, if the patient is given a highly complex mechanical puzzle to solve, the patient may learn it as quickly as a normal person, but on questioning will not remember seeing the puzzle or having worked on it previously. When H.M. is asked what he remembers of a particular task, he will deny learning the task even when his response reveals good learning and memory. Thus, when a patient such as H.M. is asked why he performs a particular task much better after five days of training than on the first day, he may respond, "What are you talking about. I've

never done this task before." As Weiskrantz comments, the patient "convincingly reveals his amnesia in his answer to the question."

The memory of amnestic patients, moreover, is not limited to the learning of motor skills. As shown by Neil Cohen and Larry Squire at the University of California in San Diego, these patients also perform normally on various perceptual tasks. In addition, they do very well with still another form of learning called priming, the facilitation of perceptual performance following prior exposure to words or visual clues. This test was first developed by Weiskrantz and Warrington in 1968. They found that if a subject was provided with visual cues he could recall or recognize the cued items better than other items for which no cues were provided. Thus, when a subject was shown fragments of previously viewed pictures or the first few letters of previously studied words, he often responded to these cues by producing the previously presented item, even though he did not recognize that the item was familiar.

Students of behavior immediately appreciated that the distinction between types of learning that emerged from studies of patients with temporal lobe lesions described a fundamental psychological distinction—a division in the way all of us acquire knowledge. In fact, in the early 1950s, Gilbert Ryle, the Oxford philosopher of mind, and Jerome Bruner, the Harvard psychologist, independently emphasized the existence of two types of knowledge systems: (1) a system concerned with knowing *how*, a reflexive knowledge of motor or perceptual skills that is recorded without keeping a conscious record of this knowledge, and (2) a system concerned with knowing *what*, a conscious knowledge of people, places, and things. Concurrently, the psychologist Endel Tulving, then at Yale University, provided the first experimental evidence for multiple memory systems through behavioral studies of normal subjects.

Explicit and Implicit Forms of Learning

The two major forms of memory are carried by distinct neural systems. Although it is still not clear exactly how many distinct memory systems there are and how they should be named, there is consensus that lesions of the temporal lobe severely impair certain forms of learning and memory that require a conscious record. Following the suggestion of Neil Cohen and Larry Squire and of Daniel Schachter, these forms of learning are commonly called declarative or explicit. Other forms of learning that do not require conscious participation remain surprisingly intact. These forms of learning are often called nondeclarative or implicit.

Learning that is called explicit is fast and may occur with one training trial; it often involves association of simultaneous stimuli and permits storage of information about a single event that happens in a particular time and place, and therefore affords a sense of familiarity about previous events. Such a representation is accessible to information-processing systems other than the one in which the learning occurred. Explicit learning importantly involves the hippocampus and the adjacent areas of the cortex. By contrast, implicit learning is slow and accumulates through repetition over many trials; it often involves association of sequential stimuli and permits storage of information about predictive relations between events. Implicit learning is expressed primarily by improved performance on certain tasks, without the subject being able to describe just what has been learned. Implicit skills involve memory systems that do not access the contents of the general knowledge of the individual. Thus, implicit memory is thought to be tied to and expressed through activation of the particular sensory and motor systems engaged by the learning task, and it is acquired and retained by the plasticity inherent in these neuronal systems. Whereas explicit memory requires structures in the temporal lobe in vertebrates, implicit memory can be studied in a variety of reflex systems in either vertebrates or invertebrates. Indeed, even simple invertebrate animals show perfectly good reflexive learning such as habituation, sensitization, classical conditioning, and operant conditioning.

There are two problems with this distinction between explicit and implicit learning. First, albeit fundamental, this distinction describes extreme cases. In many instances of learning, both implicit and explicit systems are used, and each of the components contributing to the learning is then processed in parallel by each of the memory systems. This notion of parallel processing in memory is important and brings the processing of memory storage in line with processing of sensory information that also is characterized by parallel pathways. In addition, a parallel-process view reconciles the conflicting views of learning held by behaviorists and those held by cognitive psychologists. By focusing on the reflexive components of behavior, behaviorists biased their research toward implicit memory tasks. By focusing on tasks requiring the acquisition of factual knowledge about people, places, and things, cognitive psychologists have biased their research toward explicit learning tasks. Clearly, mammals and humans acquire both types of knowledge and frequently acquire them concurrently. Second, this distinction emerged from human studies, where it is easy to determine the degree of conscious awareness required for a given mem-

ory task. In experimental animals this is more difficult. There is now good evidence, however, that a number of complex tasks for animals, in particular those that require spatial orientation, seem to embody features of explicit memory in humans and require the temporal lobe system

Changes in the Strength of Synaptic Connections

Nevertheless, the existence of two distinct forms of learning has caused the reductionists among neurobiologists to ask: Given that memory for any form of learning involves many nerve cells, is there a representation on the cellular level for each of these two types of learning processes? If so, are there distinct sets of learning rules for each type? Despite their differences, implicit and explicit forms of learning do share common features. As first pointed out by Aristotle and subsequently emphasized by the British empiricist philosophers Locke, Hume, and Mill, we learn most new information about the world by association—by connecting the new idea with a previously stored idea. In fact, many explicit and implicit tasks involve associative forms of learning. Therefore, both the neural systems that mediate explicit and those that mediate implicit memory must be capable of storing information about the association of stimuli. This raises the questions: What are the cellular learning rules whereby associations are stored in each of these two types of memory systems? Are there different cellular rules for each system? Or is there a set of common cellular rules used in various combinations in both systems?

A common assumption underlying early studies of the neural basis of memory systems is that the storage of associative memory requires a fairly complex neural circuit. One of the first people to challenge this view was the Canadian psychologist Donald Hebb, a teacher of Brenda Milner. Hebb boldly suggested that associative learning could be produced by a simple cellular mechanism. He proposed that associations could be formed by coincident activity: "When an axon of cell A is near enough to excite a cell B and repeatedly or persistently takes part in firing it, some growth process or metabolic change takes place in one or both cells such that A's efficacy, as one of the cells firing B, is increased." According to Hebb's learning rule, coincident activity in the presynaptic and postsynaptic neurons is critical for strengthening the connection between them (a pre-post associative mechanism).

Ladislav Tauc and Kandel proposed a second associative learning rule in 1962 while working at the Institute Mary in Paris on the nervous system of the marine snail Aplysia. They found that the

synaptic connection between two neurons could be strengthened without requiring the activity of the postsynaptic cell, when the action of a third neuron (which is called a modulatory neuron) acts on the presynaptic neuron so as to enhance transmitter release from its terminals, a process called heterosynaptic facilitation. They suggested that this heterosynaptic mechanism could take on associative properties if action potentials in the presynaptic cell were coincident with action potentials in the modulatory neuron that synapses on the presynaptic neuron (a pre-modulatory associative mechanism).

Subsequently, Robert Hawkins, Thomas Carew, Thomas Abrams, and Kandel at Columbia University and Edgar Walters and Jack Byrne at the University of Texas in Houston found that this pre-modulatory associative mechanism occurs in Aplysia, where it contributes to classical conditioning, an implicit form of learning. In turn, Holger Wigstrom and Bengt Gustafsson, working at the University of Goteborg in Sweden, found that the Hebbian pre-post coincidence mechanism occurs in the hippocampus, where it is utilized in forms of synaptic change that are important for spatial learning, an explicit form of learning. The finding of two distinct cellular learning rules, each with associative properties, suggested that the associative specificity of implicit and explicit learning need not require a complex neural network. Rather the ability to detect associations may simply reflect the intrinsic associative capability of certain cellular interactions.

These analyses of changes in synaptic efficacy thought to contribute to implicit and explicit forms of learning raise two surprising reductionist possibilities. First, associative heterosynaptic facilitation in Aplysia partakes of a mechanism that also is used for a nonassociative form of facilitation. Similarly, LTP in the hippocampus evidently partakes of both a Hebbian mechanism and a non-Hebbian mechanism similar to that seen in Aplysia. These results suggest there may be a cellular alphabet for synaptic plasticity, by which some elements are unique and others are shared, with more complex forms of plasticity using elaborations or combinations of the basic elements. Second, the fact that associative synaptic changes do not require complex neural networks suggests there may be a direct correspondence between these associative forms of learning and basic cellular properties. In both cases we have described, the cellular properties seem to derive in turn from the properties of specific proteins (i.e., adenylyl cyclase and the NMDA receptor) that are capable of responding to two independent signals, such as those from the conditioned stimulus and unconditioned stimulus in conditioning. Of course, these associative mechanisms

do not act in isolation. They are embedded in cells that have rich molecular machinery for elaborating the associative process. In turn, the cells are embedded in complex neural networks with considerable redundancy, parallelism, and computational power, which add substantial complexity to these elementary mechanisms.

Long-Term Memory and Structural Changes

This brings us to one final set of questions: How long do the synaptic changes produced by explicit and implicit learning last? How are they maintained? Experiments in both Aplysia and in mammals indicate that explicit and implicit forms of memory storage proceed through stages and that the same synaptic sites that store the initial information relevant for short-term memory, which lasts from minutes to hours, also store long-term memory over a period of days and weeks. Whereas short-term changes in synaptic strength involve changes in the efficacy of preexisting synaptic connections by means of second-messenger-mediated covalent modifications of preexisting proteins, the long-term changes require gene activation of new protein synthesis and the growth of new connections. For example, Craig Bailey, Mary Chen, and their colleagues at Columbia and Byrne and his colleagues at the University of Texas in Houston have shown that stimuli producing long-term memory for nonassociative forms of learning, such as sensitization, as well as associative forms of learning, such as classical conditioning, lead to an increase in the number of presynaptic terminals.

If long-term memory leads to anatomical changes, does this imply our brains are constantly changing anatomically as we learn and as we forget? Will we experience changes in our brain anatomy as a result of reading and remembering the papers of this symposium? This question has now been addressed by a number of investigators, perhaps most dramatically by Michael Merzenich at the University of California in San Francisco, who examined the representation of the hand area in the cerebral cortex. Until recently, we believed this representation was stable throughout life. The studies by Merzenich and his colleagues now demonstrate that cortical maps are subject to constant modification based on use of the sensory pathways. Since all of us are brought up in somewhat different environments, are exposed to different combinations of stimuli, and are likely to exercise our sensory and motor skills in different ways, the architecture of each of our brains will be modified in slightly different ways. This distinctive modification of brain architecture, along with a distinctive genetic makeup, contributes to the biological basis for the expression of individuality.

This view is best demonstrated in two studies by Merzenich. First, he studied normal animals and found that the topographical maps vary considerably from one individual to another. This study, of course, did not separate the effects of different experiences from the consequences of different genetic endowment. Therefore Merzenich, William Jenkins, and their colleagues next investigated the factors that underlie this variability. They encouraged monkeys to use their middle three fingers at the expense of other fingers by having them obtain food by contacting a rotating disc with only the middle fingers. After several thousand disc rotations, the area in the cortex devoted to the middle three fingers was expanded. Practice, therefore, may lead to changes in the cortical representation of the most active fingers.

What mechanisms underlie the changes? Recent evidence suggests the input connections to cortical neurons in the somatic sensory system (as in the visual system) may be formed in development on the basis of correlated activity, apparently similar to the mechanisms in the hippocampus that contribute to learning. Merzenich and his colleagues tested this idea by surgically connecting the skin surfaces of the fingers of two adjacent digits on the hand of a monkey. This procedure assures that the connected fingers are always used together and therefore increases the correlation of inputs from the skin surfaces of the adjacent fingers. Increasing the correlation of activity from adjacent fingers in this way abolished the sharp discontinuity normally evident between the zones in the area of the cortex receiving inputs from these digits. Thus, the normal discontinuity in the representation of adjacent fingers in the cortical map appears to be established not only by a genetically programmed demarcation in the pattern of connections but through learning by temporal correlations in patterns of input.

These early results from the cell biological studies of learning suggest the mechanisms of learning may carry with them an additional bonus. There is now reason to believe that development and learning are interrelated and may share mechanisms in common. Both are accompanied by associative changes in the effectiveness of neural connections leading to structural changes. Some of the mechanisms used for the structural changes during learning seem similar to those used during development to fine tune the initial connections formed between neurons. If this is true on the molecular level, if aspects of growth, development, and learning share molecular mechanisms in common, then molecular biology may in the long run help unify cognitive psychology and neurobiology, much as it is currently unifying neurobiology and the other biological sciences. In

so doing, molecular biology may succeed in helping to demystify the study of mental processes and position them squarely within the evolutionary framework of cell and systems biology.

The Role of Social and Biological Processes

The demonstration that learning is accompanied by changes in the effectiveness of neural connections suggests a new view of the relationship between social and biological processes in the generation of behavior. There is a tendency in medicine and psychiatry to think biological and social determinants of behavior act on separate levels of the mind. For example, it is still customary to classify psychiatric illnesses into two major categories: organic and functional. Organic mental illnesses include the dementias and the toxic psychoses; functional mental illnesses include the various depressive syndromes, the schizophrenias, and the neurotic illnesses. This distinction dates to the nineteenth century, when neuropathologists examined the brains of patients coming to autopsy and found gross and readily demonstrable disturbances in the architecture of the brain in some psychiatric diseases but not in others. Diseases producing anatomical evidence of brain lesions were called organic; those lacking these features were called functional.

The experiments reviewed in this chapter show this distinction is unwarranted. Everyday events—sensory stimulation, deprivation, and learning—can cause an effective disruption of synaptic connections under some circumstances and a reactivation of connections under others. Therefore, the view that certain diseases (organic diseases) affect mentation by producing biological changes in the brain, whereas other diseases (functional diseases) do not, is incorrect. The basis of contemporary neural science is that all mental processes are biological and any alteration in those processes is organic.

Rather than making the distinction along biological and nonbiological lines, a more appropriate question for each type of mental illness is: To what degree is this biological process determined by genetic and developmental factors, to what degree is it determined by a toxic or infectious agent, and to what degree is it environmentally or socially determined? Even those mental disturbances considered most socially determined must have a biological aspect, since it is the activity of the brain that is being modified. Insofar as social intervention works, whether through psychotherapy, counseling, or the support of family or friends, it must work by acting on the brain, and quite likely on the strength of connections between nerve cells. Moreover, the absence of demonstrable structural changes does not rule out the possibility that important

biological changes are nevertheless occurring. They may simply be undetectable with the techniques available to us.

The work of David Hubel and Torsten Wiesel and the studies by Craig Bailey, William Greenough and their colleagues make clear that demonstrating the biological nature of mental functioning will require more sophisticated anatomical methodologies than the light-microscopic histology of nineteenth-century pathologists. To clarify these issues it will be necessary to develop a neuropathology of mental illness that is based on anatomical function as well as on anatomical structure. Various new imaging techniques, such as positron emission tomography and magnetic resonance imaging, have opened the door to the noninvasive exploration of the human brain on a cell-biological level, the level of resolution that is required to understand the physical mechanisms of mentation and of mental disorders. As we have seen, this approach is now being pursued in the study of schizophrenia.

Since structural changes in mental functions are likely to reflect alterations in gene expression, we should look for altered gene expression in all persistent mental states, normal as well as disturbed. There is now substantial evidence that the susceptibility to major psychotic illnesses—schizophrenia and manic-depressive disorders—is heritable. These illnesses reflect heritable alterations in the nucleotide sequence of DNA, leading to abnormal messenger RNA and abnormal protein. Whereas the genetic data on schizophrenia and depression indicate these diseases involve alteration in the structure of genes, the cell-biological data on learning and long-term memory reviewed here suggest that neurotic illnesses, acquired by learning, are likely to involve alterations in the regulation of gene expression.

Development, hormones, stress, and learning are all factors that alter gene expression by modifying the binding of transcriptional activator proteins to each other and to the regulatory regions of genes. At least some neurotic illnesses (or components of them) are likely to result from reversible defects in gene regulation, which are produced by learning and which may be due to altered binding of specific proteins to certain regulatory regions controlling the expression of certain genes.

According to this view, schizophrenia and depression result primarily from heritable genetic changes in neuronal and synaptic function in a human population carrying one or more—likely several—abnormal alleles. In contrast, neurotic illnesses might result from alterations in neuronal and synaptic function produced by environmentally induced alterations in gene expression. An intriguing

idea, then, is that insofar as psychotherapy is successful in bringing about substantive changes in behavior, it does so by producing alterations in gene expression.

A corollary to these arguments is that a neurotic illness involves alterations in neuronal structure and function just as psychotic illnesses involve structural (anatomical) changes in the brain. Treatment of neurosis or character disorders by psychotherapeutic intervention should, if successful, also produce structural changes. Thus, we face the intriguing possibility that as brain imaging techniques improve, these techniques might ultimately be useful not only for diagnosis of various neurotic illnesses but also for evaluating the outcome of psychotherapy.

The work of our laboratories is supported in part by the Howard Hughes Medical Institute and by NIMH grants Nos. MH45923 and MH26212 and NIH grant No. AG08702.

Suggested Readings

Hawkins, R.D., T.W. Abrams, T.J. Carew, and E.R. Kandel. 1983. A cellular mechanism of classical conditioning in Aplysia: Activity-dependent amplification of presynaptic facilitation. *Science* 219:400–05.

Hawkins, R.D., E.R. Kandel, and S.A. Siegelbaum. 1993. Learning to modulate transmitter release: Themes and variations in synaptic plasticity. *Annual Review of Neuroscience* 16:625–65.

Kandel, E.R., and R.D. Hawkins. 1992. The biological basis of learning and individuality. *Scientific American* 267(3):78–86.

Merzenich, M.M., E.G. Recanzone, W.M. Jenkins, T.T. Allard, and R.J. Nudo. 1988. Cortical representational plasticity. In *Neurobiology of Neocortex*, ed. P. Rakic and W. Singer, 41–67. New York: Wiley.

Milner, B. 1966. Amnesia following operation on the temporal lobes. In *Amnesia*, ed. C.W.M. Whitty and O.L. Zangwill, 109–33. London: Butterworths.

Nicoll, R.A., J.A. Kauer, and R.C. Malenka. 1988. The current excitement in long-term potentiation. *Neuron* 1:97–103.

Squire, L.R. 1987. *Memory and brain*. New York: Oxford University Press.

MEMORY AND BRAIN SYSTEMS

Larry R. Squire

Neuroscience concerns itself with two great problems, the brain's "hard-wiring" and its capacity for plasticity. The former refers to the issue of how connections develop between cells, how cells function and communicate with each other, and how the functions we are born with—such as sleep-wake cycles, hunger and thirst, and the ability to perceive the world through five sensory modalities—are organized. Nervous systems have inherited, through millions of years of evolution, many capabilities important for survival, adaptations that are too important to be left to the vagaries of individual experience. The capacity for plasticity refers to the fact that nervous systems also inherit the ability to adapt or change as the result of experiences that occur during an individual lifetime. The experiences we have can modify the nervous system, and we can later behave differently as a result. This capacity gives us the ability to learn and to remember.

All the animals, all the brains, illustrated in figure 1 have the capacity for plasticity. One notes the gradual increase in the size of the brain with evolution of the more recent vertebrates. Nevertheless, in all of them, we find the same nameable areas and, as a first approximation, the same pattern of connectivity. Someone examining and comparing these brains in histological detail might be more impressed with the similarities than the differences. It is important to note, however, that the monkey brain is only one-tenth the size of the human brain. Also, the chimpanzee, shown in figure 1, is a protected species. No chimpanzees currently are being imported, and virtually none are used in neuroscience research. For many years, however, the monkey has been a precious and valuable experimental animal for study of the nervous system.

All the brains illustrated in figure 1 are made up of a wide variety of individual cells or neurons (figure 2). When sketched out

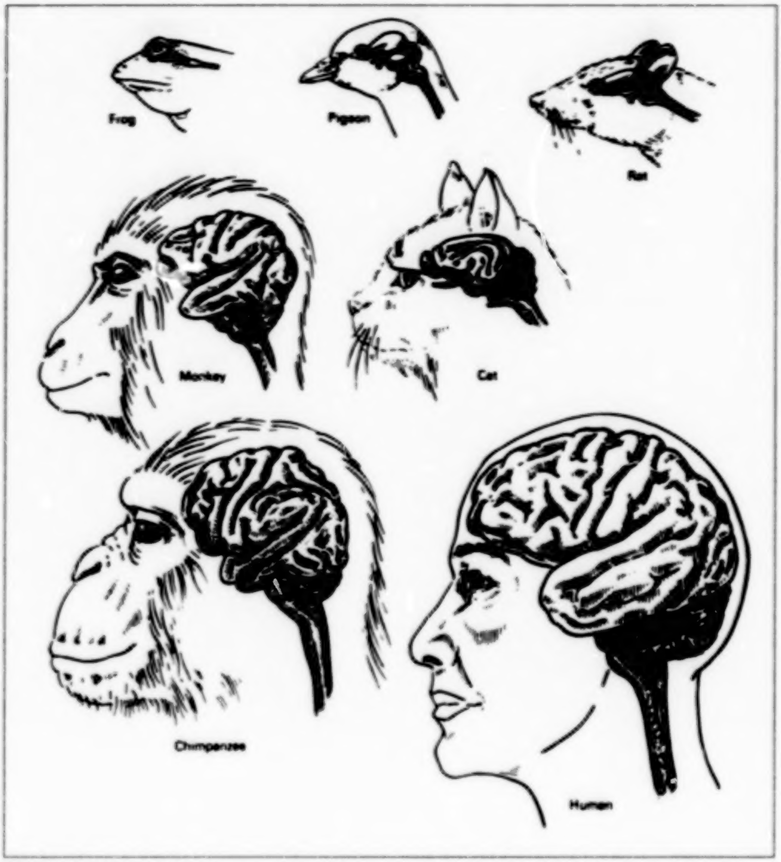

Figure 1. The brains of several vertebrate species, ranging from the frog through the monkey to the human, are illustrated. (From M.R. Rosenzweig and A.L. Leiman. 1982. *Physiological Psychology*. Lexington: D.C. Heath & Co.)

as individual entities, they appear rather like trees and flowers. All vertebrate brains contain these same basic cell types, and of course the cellular and molecular biology of the individual neurons is much the same from species to species—one manifestation of the universality of biology. Thus, neuroscientists suppose that differences between species, differences for example in cognitive ability and in memory, are probably due to the number of neurons and to the details of how they are connected with each other.

From a biological point of view, the problem of memory is sometimes recast as a problem of neural plasticity. In this context, significant progress has been made in understanding how neurons show history-dependent behavior, that is, how neurons respond

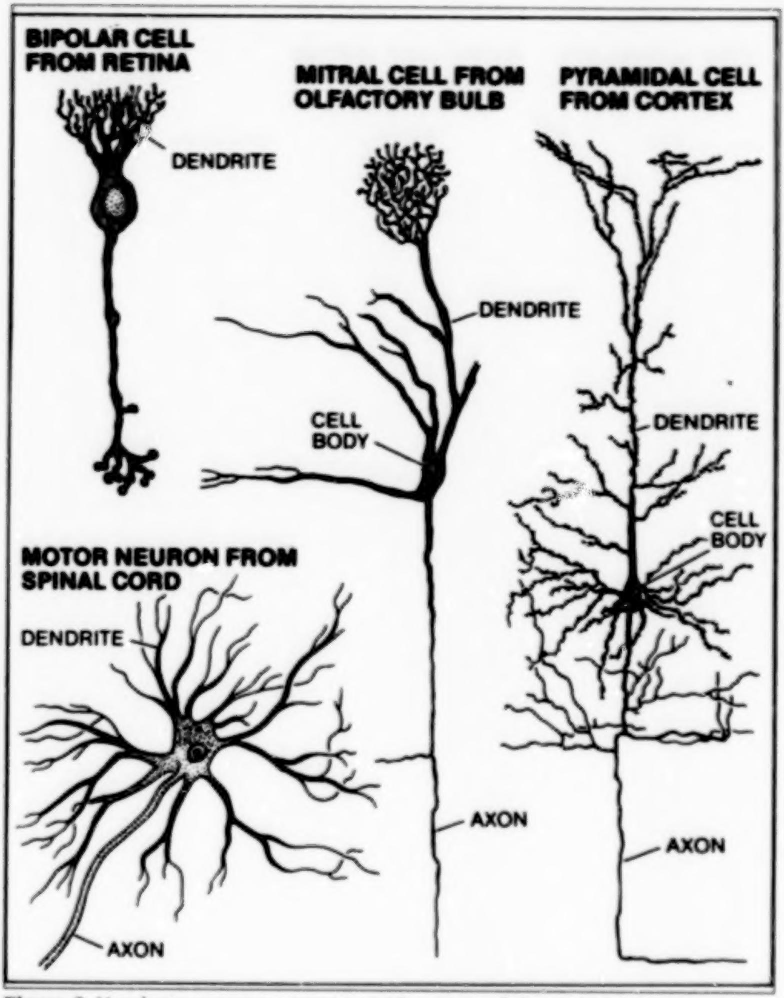

Figure 2. Vertebrate neurons come in a wide variety of shapes and sizes. (From S.W. Kuffler and J.G. Nicholls. 1976. *From Neuron to Brain*. Sunderland, England: Sinauer Associates, Inc.)

differently as a function of their past input. Yet, for better or worse, one must also address questions about how neurons operate in networks and systems to support memory and about the organization of memory as it is expressed in whole behavior. Indeed, many important questions about memory are systems-level questions that address a relatively global level of analysis. In other words, even if one understood how synapses change to alter the connectivity between neurons, many other questions would remain. Is there one

kind of memory or many? What are the brain structures and pathways involved in memory and what jobs do they do? To provide a sketch of our current understanding, I consider here three issues, illustrating each with some examples.

First, the brain is organized such that memory is a distinct and separate cognitive function, which can fruitfully be studied in isolation from perception and other intellectual abilities. Particular brain structures, including the hippocampus, are essential for the ability to lay down in memory an enduring record of experience. Damage to these structures causes an amnesic syndrome, a circumscribed impairment in the ability to learn and remember. Although significant information has come from the study of human patients, the bulk of our understanding about the anatomy of memory continues to come from the kind of systematic and cumulative work made possible only in experimental animals.

Second, memory is not a single faculty of the mind but is composed of multiple separate systems. That is, there is more than one kind of memory, not just in a semantic or philosophical sense but in the specific biological sense that different kinds of memory have different brain organizations and depend on different brain systems. The major distinction is between conscious knowledge of facts and events, which is impaired in amnesia, and other nonconscious knowledge systems that provide for the capacity of skill learning, habit formation, the phenomenon of priming, and certain other ways of interacting with the world.

Third, new technology, including positron emission tomography (PET), is providing direct anatomical and functional information about memory in living human subjects.

Amnesia and the Anatomy of Memory

The modern era for this problem began in 1953 when a patient, who was to become known as H.M., sustained a neurosurgical procedure intended to relieve severe epilepsy. The surgery involved the bilateral removal of the inner surface of the temporal lobe for a rostrocaudal distance of approximately 8 cm (figure 3). The surgery was successful in relieving the epilepsy to a point where it could be controlled by medication, but it also resulted in an unexpected and severe memory impairment for day-to-day events. H.M., who was twenty-seven years old at the time of surgery, retained an above-average intellectual ability (IQ), intact immediate (digit span) memory, intact knowledge from early life, and a personality that according to the family was unchanged by

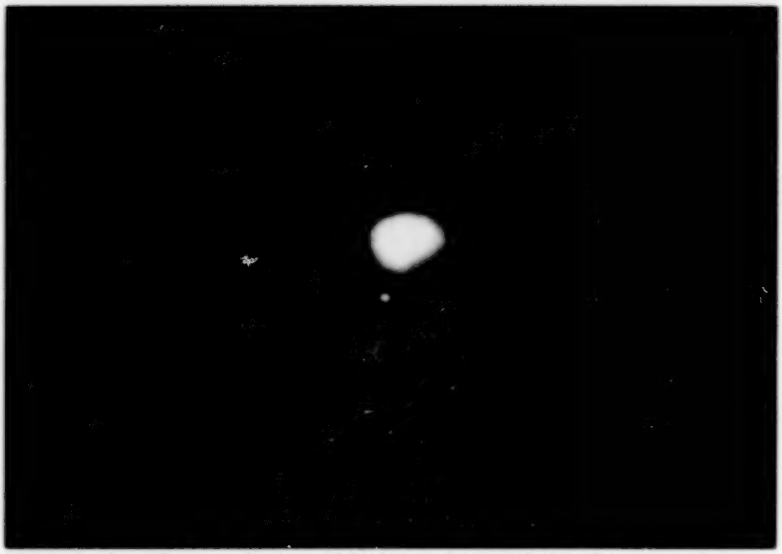

Figure 3. This schematic drawing of the human brain indicates the presumed extent of surgical removal in the well-known amnesic patient H.M. (Courtesy of Dr. David Amaral.)

surgery. Currently, in the early 1990s, H.M. is in his late sixties and remains an active participant in research. The case taught two important principles about how the brain accomplishes learning and memory. First, the medial temporal lobe is important for memory function. Second, the brain has to some extent separated perceptual processing and other intellectual processing functions from the capacity to lay down an enduring record of the memories that ordinarily result from such processing.

This case is often cited as providing evidence that the hippocampus is important for memory. As figure 3 indicates, H.M.'s lesion, while including the hippocampus, also involved a number of adjacent areas: the amygdala, parahippocampal cortex, entorhinal cortex, and perirhinal cortex. Emphasis was placed initially on the posterior half of the lesion, because other patients who underwent temporal lobe surgery appeared to develop memory impairment only when the removal extended far enough posteriorly to include the hippocampus and the underlying cortex. Nevertheless, many years passed before investigators could determine which brain structures within H.M.'s large lesion were the crucial ones important for memory function.

Two major developments contributed to progress on this problem. First, anatomical information became available from two carefully studied single cases of memory impairment. These two cases, which became available in the 1980s, provided strong and direct evidence for the importance of the hippocampus itself in human memory. The second development was the establishment in the early 1980s of an animal model of human memory impairment in the monkey. The animal model set the stage for identifying the major structures and connections in the medial temporal lobe important for memory, and this was eventually achieved after about 10 years of experimental work.

The first of the just-mentioned human cases was patient R.B. In 1978 R.B. developed memory impairment at the age of fifty-two following an episode of global ischemia that occurred as a complication of open-heart surgery. He recovered from the ischemic event and survived for five years, during which time the only detectable cognitive deficit was a moderately severe memory impairment (figure 4). Upon his death, thorough histological examination revealed a restricted bilateral lesion involving the entire rostrocaudal extent of the CA1 field of the hippocampus. Studies of experimental animals have indicated the CA1 field is particularly vulnerable to ischemic damage. Moreover, the anatomical facts of hippocampal circuitry mean that damage restricted to the CA1 region of the hippocampus would disrupt the flow of information into and out of the hippocampus. These findings suggested that the hippocampus itself is a critical component of the medial temporal lobe memory system. Subsequently, a second case of memory impairment was described in which the pathology also was limited to the hippocampus bilaterally.

In the early 1980s investigators began to pursue these same problems systematically in the monkey. Monkeys could be prepared with bilateral surgical lesions of particular brain structures and their memory evaluated quantitatively using specially designed tasks. Although many tasks have been used to assess memory in monkeys, the one most widely used has been the delayed nonmatching-to-sample task. In this test, a single object is presented to the monkey and then after a short delay two objects are presented, the original object and a novel one. To obtain a raisin reward, the monkey must select the novel object. New pairs of objects are used on each trial. Human amnesic patients perform poorly on the delayed nonmatching-to-sample task when the task is administered to patients exactly as it is administered to monkeys. Indeed, a number of parallels now have been demonstrated between human amnesic

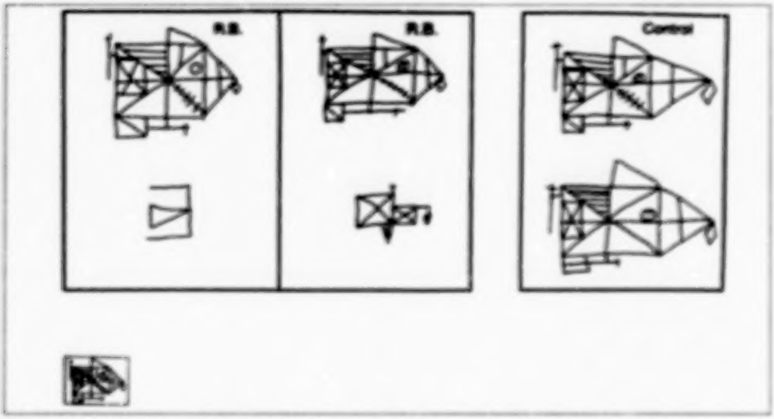

Figure 4. Amnesic patient R.B. was tested on two separate occasions with the Rey-Osterreith complex figure test. He was asked to copy the figure illustrated in the small box to the lower left. Then, without forewarning, he was asked to reproduce the figure from memory ten to twenty minutes later. The left panel shows R.B.'s copy *(top)* and his reproduction *(bottom)* six months after the onset of his amnesia. The middle panel shows R.B.'s copy and reproduction twenty-three months after the onset of his amnesia. The right panel shows the copy and a reproduction of a healthy normal subject matched to R.B. for age and education. This normal subject's data were selected as average from a group of six normal subjects. (From S. Zola-Morgan, L.R. Squire, and D.G. Amaral. 1986. Human amnesia and the medial temporal region: Enduring memory impairment following a bilateral lesion limited to field CA1 of the hippocampus. *Journal of Neuroscience* 6:2950-67.)

patients and monkeys with lesions of the medial temporal lobe, including monkeys with lesions intended to mimic the damage sustained by patient H.M.

Cumulative study of monkeys using tasks such as delayed nonmatching to sample have led to three main conclusions. First, the amygdala is not part of the medial temporal lobe memory system. Experiments with both rats and monkeys suggest that the amygdala is important in other functions, including the elaboration of emotional behavior, fear conditioning, and the attachment of affect to neutral stimuli. Second, the hippocampus is an essential component of the system. Third, structures adjacent to and anatomically related to the hippocampus are also important (entorhinal, perirhinal, and parahippocampal cortex), and these structures together with the hippocampus constitute the full medial temporal lobe memory system (figure 5).

The medial temporal lobe is not the only area of the brain where damage can cause severe memory impairment. Bilateral damage in the diencephalon, especially in the medial thalamus, also can result in amnesia. The important structures appear to be

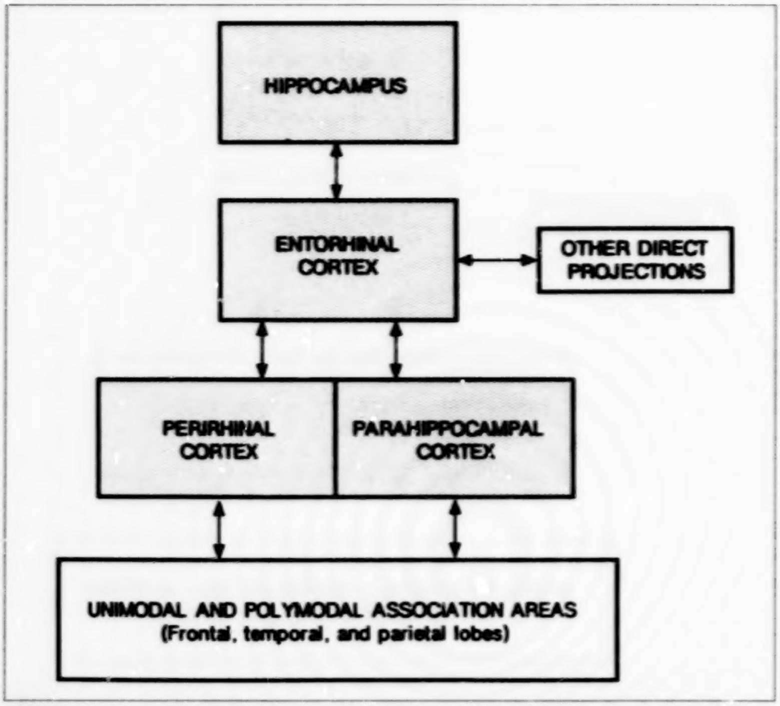

Figure 5. The components of the medial temporal lobe memory system are shown as shaded boxes. The entorhinal cortex is the major source of projections to the hippocampal region (hippocampus proper, dentate gyrus, and subicular complex). Nearly two-thirds of the cortical input to the entorhinal cortex originates in the adjacent perirhinal and parahippocampal cortices, which in turn receive input from unimodal and polymodal areas in the frontal, temporal, and parietal lobes. The entorhinal cortex also receives other direct projections from orbital frontal cortex, cingulate cortex, insular cortex, and superior temporal gyrus. All these projections are reciprocal. (From L.R. Squire, and M. Zola-Morgan. 1991. The medial temporal lobe memory system. *Science* 253 (September 20):1380–86. Copyright 1991 by the AAAS.)

the mediodorsal nucleus of the thalamus, the anterior thalamic nucleus, and the internal medullary lamina. Diencephalic amnesia resembles medial temporal lobe amnesia in many ways, and these two entities cannot yet be distinguished based on behavioral criteria. Both brain regions can be considered as crucial parts of a limbic/diencephalic system important for memory.

Multiple Forms of Memory

One of the profound insights to emerge in the past decade is that memory is not a single entity but is composed of several different abilities. Before this development, memory was understood

to vary in strength and accessibility and to be capable of being expressed in various tasks, but it was still conceptualized as a single biological and psychological phenomenon. Memory was a special case of neural plasticity, dependent on synaptic change, whereby experience leads to a change in behavior. The unitary view now has been replaced by the notion that multiple memory systems exist in the brain.

Some of the most compelling evidence for the newer view has come from findings that amnesic patients, who are severely impaired on conventional memory tests that assess recall and recognition of previously encountered material, are nevertheless fully intact at many kinds of learning and memory. They are impaired at remembering facts and events (declarative memory), but they are intact at skill learning, certain kinds of conditioning, and habit learning, and they are intact as well at the phenomenon of priming (figure 6). This distinction is not just a recounting of what amnesic patients can and cannot do. Several independent lines of evidence suggest amnesia has revealed a biologically natural division in how the nervous system has organized its capacity for acquiring, storing, and retrieving information. An important implication of this idea is that the limbic/diencephalic structures, which when damaged produce severe and disabling amnesia, have a more limited role in memory than once believed. They are involved in the acquisition of

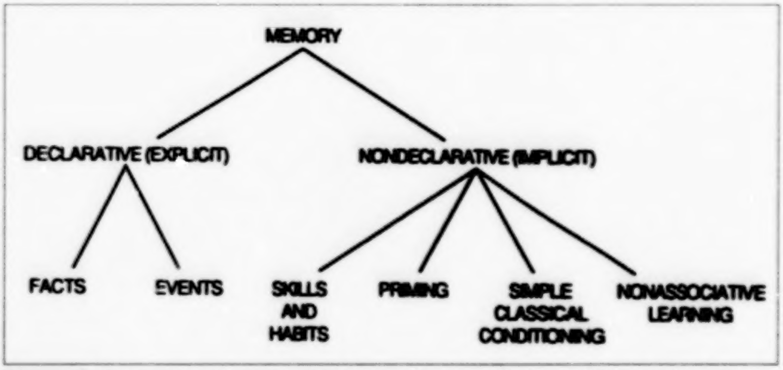

Figure 6. Declarative memory refers to conscious recollection of facts and events and depends on the integrity of limbic/diencephalic structures. Nondeclarative memory refers to a heterogeneous collection of abilities. In the case of nondeclarative memory, experience alters behavior nonconsciously without providing access to any memory content. (From L.R. Squire and M. Zola-Morgan. 1991. The medial temporal lobe memory system. *Science* 253 (September 20):1380–86. Copyright 1991 by the AAAS.)

declarative knowledge (fact and event memory) that is available as conscious recollection.

Nondeclarative memory is a heterogenous collection of abilities, all of which are independent of the limbic/diencephalic brain structures damaged in amnesia. Nondeclarative memory is nonconscious. Information is acquired as changes within specific perceptual or response systems or as changes encapsulated within specific knowledge systems without affording access to any prior conscious memory content and independent of conscious memory for the prior encounters that led to behavioral change. The rich variety of nondeclarative memory abilities can be appreciated by considering the sorts of tasks amnesic patients can acquire normally. Intact performance in amnesic patients has been documented in motor-skill learning, in tasks of perceptual skill learning (such as learning to read mirror-reversed text), and in tasks of cognitive-skill learning (such as the ability to improve at certain computer-based problems).

Very specific information about prior encounters can be supported by nondeclarative memory. For example, amnesic patients exhibited intact acquisition and retention of a text-specific reading skill. Reading of text aloud increased the speed with which the same text was subsequently read, but no facilitation occurred for new text. Amnesic patients also exhibited normal shifts in preference or judgment following exposure to novel verbal and nonverbal material, normal adaptation-level effects, and intact long-lasting priming effects for the names of objects that were specific to the particular objects presented.

In the case of object priming, subjects first were shown pictures of simple objects, one at a time, and asked to name each picture as quickly as possible. Then, either two or seven days later, subjects were shown more pictures and were asked again to name them as quickly as possible. The results indicated both amnesic patients and normal subjects named the old pictures substantially faster than the new pictures. The new pictures were named with a latency of 1110 msec, and the old pictures were named with a latency of 986 msec. Moreover, when a different version of the original picture was used, but one that had the same name (e.g., a picture of a beagle instead of a retriever, both of which would be identified as dog), the facilitatory effect was significantly reduced (naming latency = 1042 msec). Thus, priming was greatest when the exact physical characteristics of the stimuli were maintained across their two presentations. This finding suggests that a substantial component of the priming effect is based on specific visual in-

formation. This priming effect, therefore, is likely to be based on changes at relatively early stages of visual information processing. They are presemantic in the sense that the effect is highly perceptual and does not require an appreciation of the name of the stimulus or what it means. In contrast to the findings for priming, amnesic patients were greatly disadvantaged when they were asked simply to identify which pictures they had seen before (79.4 percent correct for normal subjects, 58.8 percent correct for amnesic patients, where chance performance equals 50 percent).

Functional Anatomy of Human Memory

Most of the available information about the anatomical structures and connections involved in memory functions has come from analysis of the effects of lesions in memory-impaired patients and experimental animals. The development of neuroimaging methods based on positron emission tomography (PET) provided the opportunity to study the anatomy of declarative and nondeclarative memory directly in normal subjects. In collaborative research with Marcus Raichle and his colleagues at Washington University, we have monitored local blood flow using the $[O^{15}]$ H_2O method while subjects performed one of several similar tasks. The strategy is to use a rapidly decaying radioisotope to monitor regional cerebral blood flow $[O^{15}]$ H_2O has a half-life of 123 sec). In this way, one can identify the distribution of radioactivity in association with different cognitive states. The image produced during one cognitive state is substracted from the image produced during a second, related state in order to isolate changes in regional blood flow associated with specific cognitive operations. To achieve this, one selects tasks carefully with the objective of manipulating only a small number of cognitive components from task to task.

In the study, eighteen normal volunteers participated in four task conditions involving four separate PET scans given during a single two-hour session. Before each scan, subjects studied fifteen common English words words four to eight letters in length, which were presented one at a time (e.g., *motel, income*). About three minutes after the words were presented, subjects saw word stems (three-letter word beginnings) one at a time. Each word stem could form at least 10 common English words (e.g., *mot, inc*). During presentation of the stems, and while local blood flow was being monitored, subjects performed one of four physically identical tasks: (1) For no response; subjects viewed the word stems but made no verbal response, and none of the stems could form words

that had been studied. (2) For the baseline response: subjects completed the word stems to form the first word to come to mind and spoke that word aloud. Again, none of the stems could form study words. (3) In priming, the response was the same as the baseline condition, except that now half of the stems could form study words. (4) Last, memory (or cued recall) was involved: subjects attempted to complete the word stems to form study words, and they spoke these words aloud. Half of the stems could potentially be completed to form study words.

The behavioral performance of the subjects resembled the performance of normal subjects who have participated in similar studies of word-completion priming. The baseline score was 7.5 percent (baseline priming was calculated as the percent of words produced that matched the list from which the word stems were taken, even though that list had not been presented). The priming score was 70.8 percent, and the memory score was 79.2 percent. Priming in this task is fully intact in amnesic patients, but the memory scores of amnesic patients are poorer than those of normal subjects.

Three major findings were derived from the PET study. Figure 7 shows one of the two largest blood flow changes in the brain resulting from the memory minus baseline subtraction for the fourteen subjects who completed these two conditions successfully without movement artifact. The locus of change was in the right posterior medial temporal lobe in the area occupied by the hippocampus and the parahippocampal gyrus. Further analysis indicated the priming task also engaged the hippocampal region to some extent (priming minus baseline, $p<.05$), perhaps because during the priming condition visual recognition could potentially occur for the familiar word stems. Indeed, most of the subjects became aware of the link between the word stems and the target words. Importantly, the memory task activated the hippocampal region to an even greater extent than the priming task (memory minus priming, $p<.05$).

That activation occurred in the ***right*** hippocampal region in a ***verbal*** memory task like the one used here may seem surprising. However, the right hemisphere appears to be more important than the left when performance is determined by the visual form of words rather than by their phonetic or semantic characteristics. This principle was established many years ago in studies of "split-brain" patients. The importance of the right hemisphere for verbal tasks also was demonstrated in recent divided visual-field studies with normal subjects designed specifically to illuminate the findings from

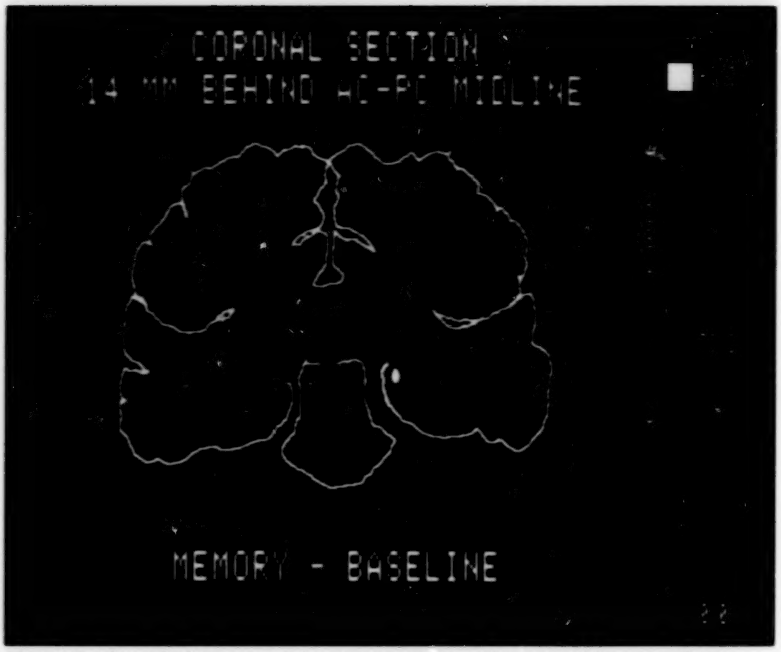

Figure 7. The right hippocampal region was activated in normal human subjects who were engaged in a memory task. The image is a 2 mm-thick coronal section 14 mm posterior to the midpoint of the line joining the anterior and posterior commissures (AC-PC midline). The section shows the major finding produced by a memory task in comparison to a baseline condition. The color scale is linear in units of PET (positron emission tomography) counts and represents increases in blood flow (60 counts = 6 percent increase). (From L.R. Squire, J.G. Ojemann, F.M. Miezin, S.E. Petersen, T.O. Videen, et al. 1992. Activation of the hippocampus in normal humans: A functional anatomical study of memory. *Proceedings of the National Academy of Sciences* 89:1837–41.)

PET. When words and word stems were presented in the same sensory modality and in the same lettercase (upper or lower), word-stem completion priming and cued recall depended more on the right hemisphere than on the left. In the PET studies, where both the words and the word stems were presented visually and always in capital letters, both priming and cued recall apparently can be supported strongly by the visual form of the word stems.

The second finding was that the right prefrontal cortex was activated in the memory condition in comparison to the baseline condition (fourteen subjects contributed to this comparison). This region exhibited little activity in any of the other task conditions compared to what was observed in a fixation-point condition that preceded the word tests. Activation of right prefrontal cortex has

been reported previously in PET studies in tasks requiring response selection. In addition, damage to prefrontal cortex impairs performance on tasks that require search strategies and sustained attention.

The third finding was, for fifteen subjects contributing to the priming minus baseline comparison, a reduction of activity in right occipital cortex in the region of the lingual gyrus (corresponding to visual area V2 or V3). This reduction of activity tended to occur as well in the memory condition (memory minus baseline, $p<.07$), presumably because the priming and memory tasks were similar with respect to the features that should be relevant for priming. Activation in this same region of right occipital cortex has been reported previously during the passive visual presentation of single words. In this case, activation was associated with the visual features of the words, not their orthographic regularity or their lexical status. These PET findings provide direct support for the idea that priming can involve rather early stage perceptual processing stations. The findings also suggest an interesting explanation for the phenomenon of repetition priming. For a time after the presentation of a word or other perceptual object, less neural activity is required to process the same stimulus.

These findings from PET illuminate two ways in which experience can modify the nervous system and influence subsequent behavior. Enhanced performance due to repetition priming depends on changes in relatively early stage visual processing centers. Which loci support priming can be expected to vary depending on the precise nature of the stimulus material and on the similarity between the material presented for study and for test. Participation of the hippocampal region and an interaction between this region and cortical representations are required for declarative memory.

Implications of Multiple Memory Systems

Conscious and nonconscious memory systems ordinarily cooperate with each other in learning, in the sense that many learning tasks are amenable to multiple strategies and to both declarative and nondeclarative kinds of learning. Thus, one's behavior toward a familiar face or stimulus object can be expected to be a combination of declaratively guided, conscious recollections about the stimulus and its significance, as well as nondeclarative, nonconscious dispositions shaped by previous encounters.

The existence of multiple memory systems has implications for traditional notions about the construct of the unconscious mind.

In considering the effects of past experience on subsequent behavior, it matters how one understands the nature of memory. By the traditional view, material that is unconscious is below some threshold of accessibility and could potentially be made available to consciousness. Yet, experimental inquiry has led to a distinction between a kind of memory that is conscious (declarative memory), which by its nature can be brought to mind, and other kinds of memory that are nonconscious in the sense that the acquired knowledge is expressed through performance without affording any awareness of memory content. In the case of nonconscious memory, early experience can affect subsequent behavior, but the mechanism by which experience persists does not include a record of the event itself. Behavior simply changes. Thus, following multiple and varied encounters, experience can result in altered dispositions, preferences, conditioned responses, habits, or skills, but these changes do not afford any potential for an awareness that behavior is being influenced by past experience. In this sense, the unconscious does not become conscious. Behavior can change by acquiring new habits that supersede old ones, or one can become sufficiently aware of the existence of a habit such that one can to some extent alter it through practice or limit the stimuli that elicit it. One does not become aware of memory content in the same sense, however, that one knows the content of a declarative memory.

Conclusion

Memory is localized in the sense that different parts of the brain store different aspects of information, but memory is distributed in the sense that multiple areas of neocortex participate in representing even simple pieces of information (figure 8). If distributed activity in the neocortex, which subserves perception and short-term memory, is to persist as stable and enduring long-term declarative memory, then at the time of learning information must converge into the medial temporal lobe memory system. Through associative mechanisms in the medial temporal lobe, conjunctions are formed and stored that are able to bind together the distributed record of a whole event. For a time after learning, these conjunctions, these sites of plasticity, retain the capacity to revivify, even from a partial cue, the separate components in neocortex that together constitute a whole memory.

Diencephalic structures, particularly medial thalamic structures, also participate in this process, perhaps as a way of accessing the frontal lobes so that conscious recollections can be translated

into action. In any case, the limbic/diencephalic system that supports declarative memory provides for the possibility of conscious recollection. Declarative memory is fallible, in the sense that forgetting can occur as well as failures of retrieval. Declarative memory is also precious, giving rise to our capacity for personal autobiography and the possibility of cultural evolution.

Other kinds of memory also exist, such as skills, habits, priming, or conditioning. These memories are acquired, stored, and retrieved without the participation of the limbic/diencephalic system and are more fundamental, phylogenetically early, and essential for survival. In contrast to declarative memory, nondeclarative forms of memory are reliable and consistent, adapted for slow and

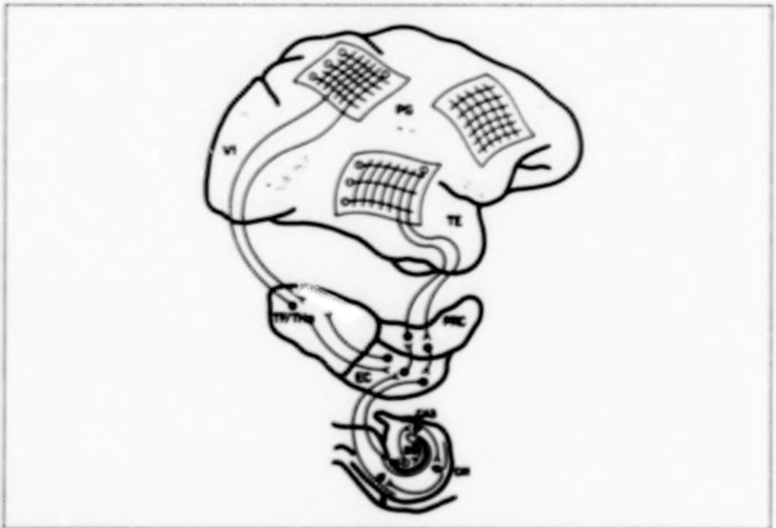

Figure 8. The components of the medial temporal lobe memory system are illustrated in this schematic drawing of the primate cortex. The networks in the neocortex show putative representations of visual object quality in the inferotemporal cortex (area TE) and of object location in the posterior parietal cortex (area PG). At the time of learning, information from the neocortex arrives initially at the parahippocampal gyrus (area TF/TH) and the perirhinal cortex (PR, areas 35 and 36), and then to the entorhinal cortex (EC, area 28), the gateway to the hippocampus. Further processing occurs in the stages of the hippocampus (the dentate gyrus [DG] and the CA3 and CA1 regions, and information ultimately exits this circuit by way of the subiculum (S) and EC, where widespread afferents return to the neocortex. Not shown here are the several projections connecting the medial temporal lobe system to medial diencephalic structures and the projections from the medial temporal lobe and diencephalic structures to the frontal lobe, which may be important for making conscious recollections available as the basis for action. (From L.R. Squire. 1990. Closing remarks in *The Biology of Memory*, ed. Squire and E. Lindenlaub, 648. Stuttgart: F.K. Schattauer Verlag.)

incremental change. These forms of memory are the basis of much of our personality and provide for myriad, nonconscious ways of responding to the world. And in no small part, by virtue of the nonconscious status of these kinds of memory, the nature of nondeclarative memory creates much of the mystery of human experience. Here arise the dispositions, habits, and preferences that are inaccessible to conscious recollection but, nevertheless, arise from experience. The results of these experiences very much influence us and are a part of who we are.

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Suggested Readings

Mishkin, M. 1982. A memory system in the monkey. *Philosophical Royal Society of London, (Biology)* 298:85–92.

Petersen, S.E., P.T. Fox, M.I. Posner, M. Mintun, and M.E. Raichle. 1988. Positron emission tomographic studies of the cortical anatomy of single-word processing. *Nature* 331:585–89.

Schacter, D.L.,C-Y Chiu, and K.N. Ochsner. 1992. Implicit memory: A selective review. *Annual Review of Neuroscience* 16:159–82

Scoville, W.B. and B. Milner. 1957. Loss of recent memory after bilateral hippocampal lesions. *Journal of Neurology and Neurosurgical Psychiatry* 20:11–21.

Squire, L.R. 1987. *Memory and brain.* New York: Oxford University Press.

Squire, L.R. 1992. Memory and the hippocampus: A synthesis from findings with rats, monkeys, and humans. *Psychological Review* 99:195–231.

Squire, L.R., B. Knowlton, and G. Musen. 1992. The structure and organization of memory. *Annual Review of Psychology* 44: 453–95, 1993.

Squire, L.R., J.G. Ojemann, F.M. Miezin, S.E. Petersen, T.O. Videen, et al. 1992. Activation of the hippocampus in normal humans: A functional anatomical study of memory. *Proceedings of the National Academy of Sciences* 89:1837–41.

Squire, L.R. and M. Zola-Morgan. 1991. The medial temporal lobe memory system. *Science* 253:1380–86.

Tulving, E., and D.L. Schacter. 1990. Priming and human memory systems. *Science* 247:301–06.

Zola-Morgan, S., L.R. Squire, and D.G. Amaral. 1986. Human amnesia and the medial temporal region: Enduring memory impairment following a bilateral lesion limited to field CA1 of the hippocampus. *Journal of Neuroscience* 6:2950–67.

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THE NEURAL BASIS OF MEMORY IN HUMANS

Antonio R. Damasio

The study of the neurological basis of mind processes such as perception, memory, or language is known as cognitive neuroscience. This discipline focuses on understanding how the brain generates the mind, a goal that has been pursued by scientists for more than a century and by philosophers for more than two millennia. Only now are we able to say that the enterprise has a chance of succeeding. As new brain imaging technologies and new experimental designs make their appearance, the ability to approach a variety of complex psychological processes increases, as does the rigor of the results. One example of a breakthrough technology is emission tomography, the main variety of which is known as positron emission tomography (PET). Using a radioactive substance, introduced in the body by means of an intravascular injection, PET maps in the human brain those regions that are more or less activated during a particular mental process.

Traditional approaches too have benefitted from technological progress and are now better suited to the needs of modern experimentation. The lesion method, which is one of the oldest in the history of neuroscience and has consistently advanced our understanding of the human brain, uses brain damage, caused by a neurological disease, to investigate the participation of a given brain area in a certain mental process. In brief, if a patient develops an area of brain damage (a "lesion") as a result of a disease (e.g., a stroke), there will be a loss of some aspect of the patient's higher psychological functions (e.g., the ability to perceive, or memorize and recall, or use language). Armed with a theory and a hypothesis about what the damaged brain region might perform in the normal brain, neuroscientists can then check whether or not the presumed ability has been lost after damage.

The modern practice of the lesion method thus requires several ingredients: first, a theory about the structure and function of the normal brain; second, a hypothesis about the function of a particular part of that normal brain; third, an experiment designed to investigate the hypothetical function; and fourth, a "lesion" in that part of the brain. The brain lesion constitutes a probe to investigate the validity of a hypothesis.

The advent of imaging methods, such as X-ray computerized tomography and magnetic resonance (MR), has led to fine detailing of the human neuroanatomy in the living human. An especially dramatic advance is a new technique to reconstruct the living human brain in three dimensions, known as Brainvox, recently developed in Hanna Damasio's laboratory. This new approach allows investigators to plot, with great precision, the exact location of an area of damage and to relate that location to the psychological process under scrutiny.

This review will outline selected developments in the field of cognitive neuroscience, focusing on the topic of memory and especially on what has been learned with the lesion method.

Memory and the Human Brain

Our understanding of the neural basis of memory began in earnest almost four decades ago with the study of patient H.M. H.M. had a surgical removal of the cerebral cortices in the inner surface of the temporal lobe, in both hemispheres. The surgery was performed to relieve H.M. of epileptic seizures which otherwise were untreatable. The operation reduced the seizures, as predicted, but it also caused a severe loss of H.M.'s ability to learn new facts. Unknown to clinicians at this time was that a bilateral resection in this region of the temporal lobe would have such a consequence. The result was entirely unexpected. The study suggested that bilateral damage to the key structures in the temporal lobe (hippocampus and the entorhinal cortex) precluded the learning of any new facts. Facts that had been learned before the surgical intervention, however, could still be recalled. Many subsequent investigations performed in patient H.M. and in other patients with disorders of learning and memory have replicated and advanced those seminal findings. Progress has been especially marked over the past decade, the highlights of which are discussed below.

As a result of his surgery, patient H.M. was unable to learn new entities and new events. It makes no difference whether the entities or events are "unique," such as one particular person or

building, or "generic," such as a person or building as a member of the broad categories of humans or buildings. The knowledge of new facts is called declarative and requires, when we retrieve it, the activation of internal representations of sensory data. There are, however, other types of knowledge. One is the perceptual and motor knowledge that enables us to perform particular actions such as riding a bicycle, or typing; it does not rely on facts but rather on skills and is called procedural. The retrieval of procedural knowledge requires a motor output, rather than an internal representation.

Patient H.M. and others who also have lost the hippocampus bilaterally can learn new skills, thus representing unequivocal proof that the hippocampal system is not required for skill learning. This pattern is evident in patients with Alzheimer's disease, in whom the memory defect is also primarily due to bilateral malfunction in the hippocampal system.

Patient H.M. retained the ability to retrieve knowledge from his past, that is, recognizing places, people, and events learned before the age of sixteen. Conversely, another famous amnesic patient, Boswell, could retrieve almost no specific knowledge from his entire past and could never place the few items he was able to recall in an appropriate temporal frame. Boswell was unable to recognize family or friends or places or objects from his past, and he could not narrate any specific episode, however important, from the several decades preceding the onset of his lesion. This specific loss of recall is known as a "retrograde" amnesia because it involves the past.

Why is Boswell's memory defect so different from H.M.'s? The answer is found in the extensive damage to "higher order" association cortices, which are not part of the hippocampal system itself and which are located in the anterior sector of both temporal regions (for instance, the sector upfront in the temporal lobe). Whereas the patient H.M. suffered damage mainly to the hippocampus, the damage in patient Boswell extended beyond the hippocampus and encompassed areas in the pole of the temporal lobe as well as in the outside and underside surfaces of the temporal lobe. The findings derived from Boswell establish that the anterior temporal cortices are necessary to access the entire range of previously acquired knowledge; a second important conclusion is that past knowledge is not permanently stored within the hippocampal system but rather outside of it.

When damage occurs in a region known as the basal forebrain, patients develop a defect of learning and retrieving that is distinguishable from the disorder caused by damage in temporal

structures. The basal forebrain region is important for various reasons. First, it contains clusters of neurons that supply the cerebral cortex with the neurotransmitter acetylcholine. Second, the region is traversed by fibers from clusters of neurons supplying the cortex with other neurotransmitters (such as dopamine and norepinephrine). Patients with damage in the basal forebrain have poor recall of material learned both after and before their lesion. The discovery of an association between basal forebrain damage and memory loss has enlarged our knowledge regarding the role structures located below the cerebral cortex must play in memory. Additional brain structures suspected to be involved in memory loss are the medial nuclei of the thalamus and the hypothalamus.

The study of defects in face learning and face recognition has offered new insights on the processes of learning and memory. For instance, face recognition and new face learning can be disrupted not only by damage within posterior visual cortices (the cortices located at the back of the brain) but also by damage within anterior temporal cortices (the cortices at the front part of the temporal region). This observation suggests the neural systems necessary for learning and recognition of faces require many components encompassing cerebral cortices placed all the way from the back to the front of the brain (e.g., early visual cortices, visual association cortices, intermediate and higher-order cortices) and the hippocampal system itself.

The study of defects in face processing has shown that patients who do not recognize any familiar face consciously can still perform nonconscious, covert recognition. Here, the strongest evidence comes from discriminatory skin conductance responses.

The most exciting new contribution of the lesion method to memory is the discovery of selective recognition defects caused by damage to the temporal cortices. Access to knowledge about entities learned through the visual sense alone and visually "ambiguous" (for instance, that share physical structures with several other different entities; typical examples are animals of the wolf family, such as fox, raccoon, and coyote, whose physical traits strongly resemble one another) depends on the inferior temporal (IT) region of both hemispheres. Knowledge of visual entities that have lesser ambiguity (e.g., an elephant or a giraffe) does not depend on this region, nor does knowledge of entities learned through both the visual and touch modalities (manipulable tools and utensils are good examples). These findings reveal that access to previously acquired generic knowledge can be disrupted by lesions in specific neural subsystems and that the defect is not equal across all types of

knowledge. These data suggest that different types of knowledge are laid down in different neural systems. The consistent allocation of certain types of knowledge to particular systems probably depends on the nature of the entities themselves and on the anatomical and functional design of the brain.

The discoveries reviewed above permit a far more detailed picture of the neural systems that underlie learning and memory than were previously available. The role of the hippocampus in learning has been reconfirmed, but the hippocampus is not essential for recall and recognition. The neural records on the basis of which we store the components generic and specific knowledge are located along complex hierarchical streams of cortical regions, placed all the way from the vicinity of the primary sensory cortices (where information arrives in the cerebral cortex) to the higher-order cortices located closer to the hippocampal system. A variety of subcortical nuclei, located in the brain stem, the basal forebrain, the medial thalamus, and the mammillary bodies, assist the above-mentioned regions during learning and retrieval. Finally, the learning and maintenance of skills do not rely on the hippocampus but depend on subcortical structures in the cerebellum and basal ganglia, together with motor and somatosensory cortices in parietal and frontal regions.

Language and the Brain

New studies with the lesion method have demonstrated the neural networks on which language processing depends include structures previously not a part of the traditional map of language-related areas. The traditional map consists of Wernicke's area, Broca's area, and the left supramarginal and angular gyri. The language map surfacing from recent lesion studies is far richer. Electrophysiological mapping of language by George Ojemann shows similar results.

The most fascinating development concerning brain and language comes from the discovery that the anterior sector of the left temporal cortices, as not previously thought, is dedicated to language. Furthermore, the systems in this territory are not concerned with all aspects of language. They are selective. They contain the mechanism of access to the reference lexicon or the collection of words denoting concrete entities and actions. Recent studies from our laboratory established the following:

(1) Damage to the left anterior temporal sector, including the temporal pole and the anterior part of the inferior temporal region,

causes a severe defect for naming of concrete entities. Patients with such lesions cannot retrieve the proper nouns that go with unique entities nor the common nouns that go with varied entities, natural or man-made, at a categorical level. However, the patients know all the entities they cannot name. No grammatical defect is present.

(2) When the lesions are confined to the most anterior part of this sector, the defect is restricted to the retrieval of proper nouns (for instance, the names of people or places). Access to most common nouns is intact, and so is access to the knowledge of the entities behind both proper and common nouns.

(3) Damage to precisely the same regions in the right hemisphere does not compromise lexical access.

(4) None of these lesions compromises the retrieval of verbs. Astonishingly, then, the selective defect in noun retrieval is not accompanied by a defect in verb retrieval and, as noted above, the patients have no defect in syntactical structure or production of grammatical functors (such as prepositions or conjunctions). The unequivocal conclusion is that the access to nouns and verbs is operated by different neural systems.

Conclusions

The last set of findings reported above is perhaps as good a witness as any that our hope of discovering the neural basis of mental activity is well founded. Several lines of investigation indeed are leading to significant progress in cognitive neuroscience.

We should also make clear that current research does more than move ahead the frontier of the life sciences. This research has immediate payoffs in clinical application and should have an influence on policy. On the clinical front, the finely etched knowledge we are gathering about brain sites and cognitive defects makes the diagnosis of neurological diseases faster and more accurate. Perhaps even more importantly, the new knowledge opens the way for developing new rehabilitation programs for those patients who are victims of stroke or other causes of brain damage, and who must cope with disabling defects in memory, or language, or decision-making. This is especially important because after brain tissue is destroyed it cannot be regenerated. The only hope of recovery is rehabilitation that consists of training suitable alternative brain areas to perform, with some other strategy, the function that has been lost.

Finally, knowing how brain and mind work, how they develop, and what can make them falter—in terms of both disease and human environment—has a bearing on educational policy and, in general, on the shaping of the cultural environment that makes humans healthy and free.

Suggested Readings

Butters, N. and L.S. Cermak. 1980. *Alcoholic Korsakoff's Syndrome.* New York: Academic Press.

Corkin, S. 1984. Lasting consequences of bilateral medial temporal lobectomy: Clinical course and experimental findings in H.M.. *Seminars in Neurology* 4:249–59.

Damasio, A. 1989a. Time-locked multiregional retroactivation: A systems level proposal for the neural substrates of recall and recognition. *Cognition* 33:25–62.

Damasio, A. 1989b. The brain binds entities and events by multiregional activation from convergence zones. *Neural Computation* 1:123–32.

Damasio, A. 1990. Category-related recognition defects as a clue to the neural substrates of knowledge. *Trends in Neuroscience* 13:95–98.

Damasio, A. 1992. Aphasia. *New England Journal of Medicine* 326:531–39.

Damasio, A., and H. Damasio. 1992. Brain and language. *Scientific American* 267:89–95

Damasio, A., and H. Damasio. 1994. Cortical systems for retrieval of concrete knowledge: The convergence zone framework. In *Large-scale neuronal theories of the brain,* ed. C. Koch, 61–74. Cambridge, Mass.: MIT Press.

Damasio, A., H. Damasio, D. Tranel, and J.P. Brandt. 1990. Neural regionalization of knowledge access: Preliminary evidence. *Symposia on Quantitative Biology.* Vol. 55. Cold Spring Harbor Laboratory, New York.

Damasio, A., and D. Tranel. 1993. Verbs and nouns are retrieved with differently distributed neural systems. *Proceedings of the National Academy of Sciences* 90:4957–60.

Damasio A, D. Tranel, and H. Damasio. 1990. Face agnosia and the neural substrates of memory. *Annual Review of Neuroscience* 13:89–109.

Damasio, H., and R. Frank. 1992. Three-dimensional in vivo mapping of brain lesions in humans. *Archives of Neurology* 49:137–43

Eslinger, P., and A. Damasio. 1986. Preserved motor learning in Alzheimer's disease. *Journal of Neuroscience* 6:3006–9.

McCarthy, R.A., and E.K. Warrington. 1988. Evidence for modality-specific meaning systems in the brain. *Nature* 334:428–30.

Milner, B., S. Corkin, and H.-L. Teuber. 1968. Further analyses of the hippocampal amnesic syndrome: 14 year follow-up study of H.M. *Neuropsychologia* 6:215–34.

Ojemann, G. 1990. Organization of language cortex derived from investigations during neurosurgery. *Seminars in the Neurosciences* 2:297–305.

Squire, L. 1987. *Memory and brain.* New York: Oxford University Press.

Language and the Brain

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CLUES TO THE NEUROBIOLOGY OF LANGUAGE

Ursula Bellugi and Gregory Hickok

In the Decade of the Brain, we stand at a new frontier in our ability to understand the biological foundations for language and other higher cognitive functions. The techniques currently available are powerful and exciting, as well as rapidly expanding. A number of techniques that were simply not available a decade ago permit us to gain precise information on the neural systems that subserve cortical functions by eavesdropping on brain structure and brain function. New studies using functional imaging (positron emission tomography, or PET among others) are telling us where in the brain linguistic and cognitive processing takes place on-line; new techniques using three-dimensional reconstruction of magnetic resonance images (MRI) now allow us to visualize directly the living brain as if we were holding it in our hands.

This three-dimensional computer reconstruction can be sliced and resliced along any dimension an infinite number of times, permitting quantitative morphological analysis in the normal brain and precise localization of nonfunctional regions in the damaged brain. Just recently, functional imaging and MRI-derived three-dimensional reconstructions have been integrated to give us three-dimensional reconstructions of the living active brain while it is engaged in cognitive activities. In the context of these and other technological advances in the Decade of the Brain, we describe a program of studies, illuminated by new techniques in brain imaging, leading toward a deeper understanding of the neural systems that subserve language and other higher cognitive functions.

Using a multidisciplinary approach we seek to gain insight into the often inaccessible workings of the brain, studying unusual languages and populations with differing cognitive and language abilities. Most of what is known about language comes from the study of spoken languages. In contrast, we have addressed dramatically different languages: the visual forms of communication that

have arisen outside of the mainstream of spoken languages. In these studies, we investigate language, its formal architecture, and its representation in the brain by studying the visual gestural systems developed among generations of deaf people. American Sign Language (ASL) displays complex linguistic structure, but, unlike spoken languages, ASL conveys much of its structure by manipulating spatial relations, thus presenting a new perspective on the determinants of language organization. This research program involves functional and structural brain imaging and the application of new experimental paradigms to determine how language is acquired, processed, and represented within the brain.

Perspectives from Language in a Different Modality

The central issues we address, namely brain organization for language and other higher cortical functions, have been illuminated by some new discoveries about the nature of language itself. Because, until recently, most of the scientific understanding of language has come from the study of spoken languages, experimental findings concerning the neural instantiation of language necessarily pertained to neurolinguistic systems only as they relate to auditory and phonetic processing. In fact, the organizational properties of language have been assumed to be connected inseparably with the sounds of speech. It has been assumed that the fact that language is normally spoken and heard determines the basic principles of grammar as well as the organization of the brain for language. Studies of brain organization indicate that the left cerebral hemisphere is specialized for processing linguistic information in the auditory-vocal mode; thus, the link between biology and behavior has been identified with the particular sensory modality in which language has developed.

Although evolution in humans has been for spoken language (there is no group of hearing people that has a sign language as its primary linguistic system), recent research into sign languages has revealed the existence of primary linguistic systems that have developed naturally in visual/manual modalities. These signed languages have all of the complexity of spoken languages and are passed down from one generation of deaf people to the next. Importantly, these sign languages are not derived from the spoken language of the surrounding community; rather, they are autonomous languages with their own grammatical form. Indeed, the sign language developed by deaf people in Great Britain is

mutually incomprehensible with the sign language developed among deaf people in the United States. The existence of these visual/manual primary linguistic systems can provide a new perspective on the determinants of brain organization for language. How is language organized when it is based instead on moving the hands in space and on visual processing? We can now investigate how the brain is organized for language when language itself is instantiated in space.

American Sign Language (ASL) exhibits formal structuring at the same levels as spoken languages and the same kinds of organizational principles as spoken languages. At the core, spoken and signed languages are essentially identical in terms of rule systems. Nevertheless, on the surface, signed and spoken languages differ markedly. The formal grammatical structuring assumed in a visual/manual language is influenced deeply at all structural levels by the modality in which the language is cast. ASL displays a complex linguistic structure, but unlike spoken languages, it conveys much of its structure by manipulating spatial relations, making use of spatial contrasts at all linguistic levels.

In our research, we have been specifying the ways in which the formal properties of language are shaped by their modalities of expression, sifting properties peculiar to a particular language mode from more general properties common to all languages. As noted, the most striking surface difference between signed and spoken languages is the reliance on spatial contrasts, most evident in the grammar of the language. Figure 1 shows some aspects of grammatical structure in ASL and its reliance on spatial contrasts. Instead of relying on linear order for inflectional marking, as in English (*act, acting, acted, acts*), ASL grammatical processes nest sign stems in spatial patterns of considerable complexity, thereby marking grammatical functions such as number, aspect, and person. Grammatically complex forms can be spatially nested, one inside the other, with different orderings producing different meanings (figure 1A). Similarly, the syntactic structure specifying relations of signs to one another in sentences in ASL is also essentially spatially organized. Nominal signs may be associated with abstract positions in a plane of signing space, and the direction of movement of the verb signs between such endpoints marks grammatical relations. Pronominal signs directed toward these previously established loci clearly function to refer back to nominals, even with many signs intervening (figure 1B). This spatial organization underlying syntax is a unique property of visual-gestural systems.

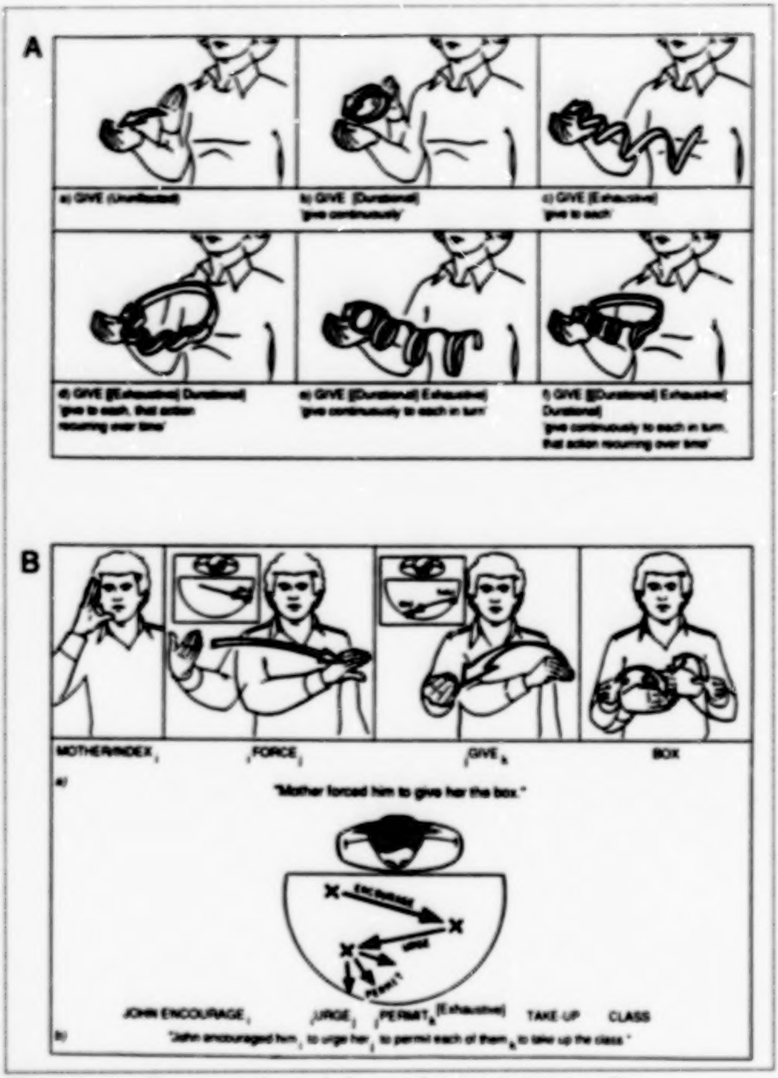


Figure 1. Spatially organized morphology and syntax in American Sign Language. (TINS)

Neural Systems Subserving a Visuospatial Language

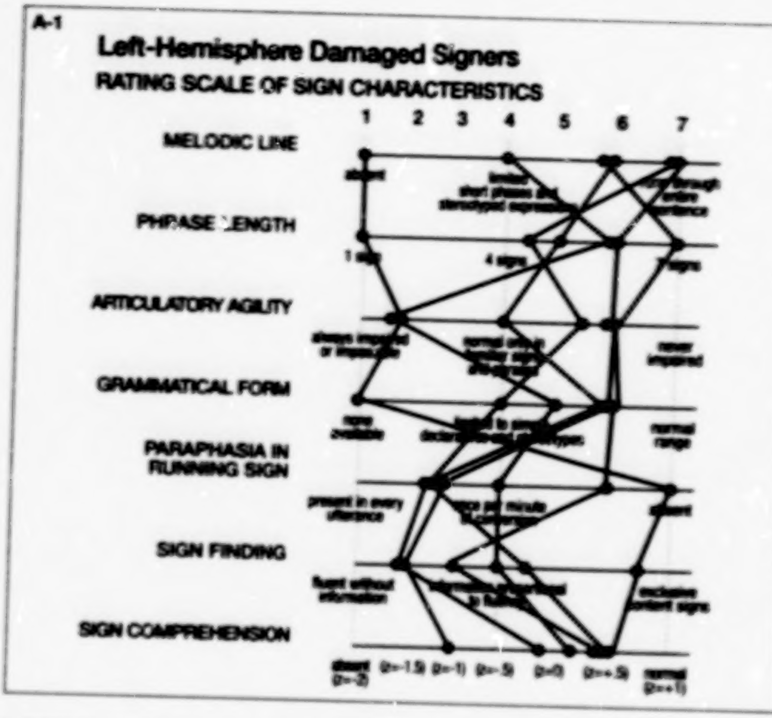
Not only is sign language independent from spoken language, it is transmitted in a different modality and encodes linguistic structure in essentially spatial distinctions rather than temporal distinctions. These differences between signed and spoken languages provide an especially powerful tool for understanding the

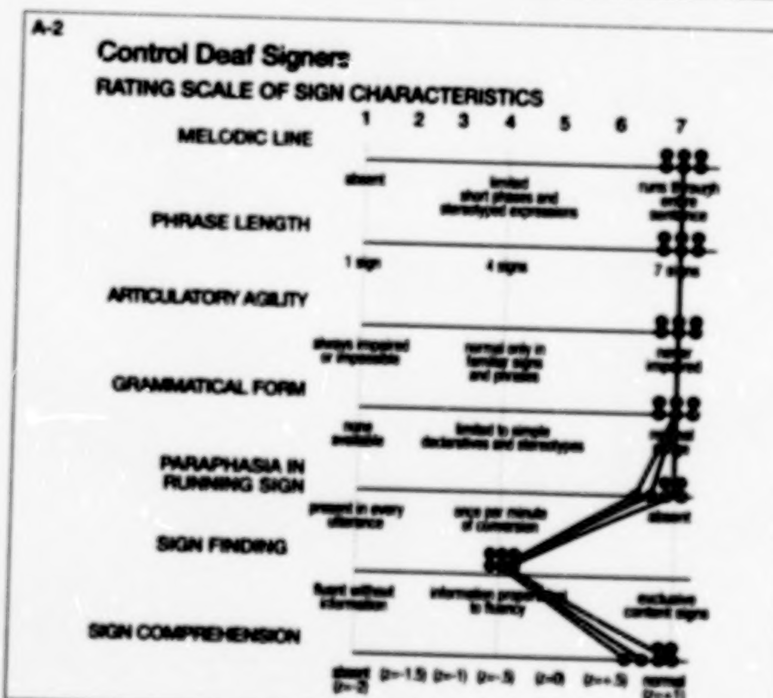
neural systems subserving language. Consider the following: In hearing/speaking individuals, language processing is mediated by the left cerebral hemisphere, whereas visuospatial processing is mediated by the right cerebral hemisphere. But what about a language that is communicated using spatial contrasts rather than temporal contrasts?

On the one hand, the fact that sign language has the same kind of complex linguistic structure as spoken languages and the same expressivity might lead one to expect left hemisphere mediation. On the other hand, the spatial medium so central to the linguistic structure of sign language clearly suggests right hemisphere mediation. The answer to the question raised is dependent on the answer to another deeper question concerning the *basis* of the left hemisphere specialization for language. Specifically, is the left hemisphere specialized for language processing per se (i.e., is there a brain basis for language as an independent entity)? Or is the left hemisphere's dominance generalized to processing any type of information presented in terms of temporal contrasts?

If the left hemisphere is indeed specialized for processing language itself, sign language processing should be mediated by the left hemisphere just as spoken language is. If, however, the left hemisphere is specialized for processing fast temporal contrasts in general, we would expect sign language processing to be mediated by the right hemisphere. The study of sign languages in deaf signers permits us to pit the nature of the signal (auditory/temporal vs. visual/spatial) against the type of information (linguistic vs. nonlinguistic) encoded in that signal as a means of examining the neurobiological basis of language.

We address these questions through a large program of studies of deaf signers with focal lesions to the left or the right cerebral hemisphere. We investigate several major areas, each focusing on a special property of the visual-gestural modality as it bears on the investigation of brain organization for language. We have now studied intensively more than twenty deaf signers with left or right hemisphere focal lesions; all are highly skilled ASL signers, and all have used sign as a primary form of communication throughout their lives. Our subjects are examined with an extensive battery of experimental probes, including formal testing of ASL at all structural levels; spatial cognitive probes sensitive to right hemisphere damage in hearing people; and new methods of brain imaging. This large pool of well-studied and thoroughly characterized subjects allows a new perspective on the determinants of brain organization for language.


A-1
Left-Hemisphere Damaged Signers
RATING SCALE OF SIGN CHARACTERISTICS
1 2 3 4 5 6 7
MELODIC LINE
PHRASE LENGTH
ARTICULATORY AGILITY
GRAMMATICAL FORM
PARAPHASIA IN
RUNNING SIGN
SIGN FINDING
SIGN COMPREHENSION


A-2
Control Deaf Signers
RATING SCALE OF SIGN CHARACTERISTICS
1 2 3 4 5 6 7
MELODIC LINE
PHRASE LENGTH
ARTICULATORY AGILITY
GRAMMATICAL FORM
PARAPHASIA IN
RUNNING SIGN
SIGN FINDING
SIGN COMPREHENSION

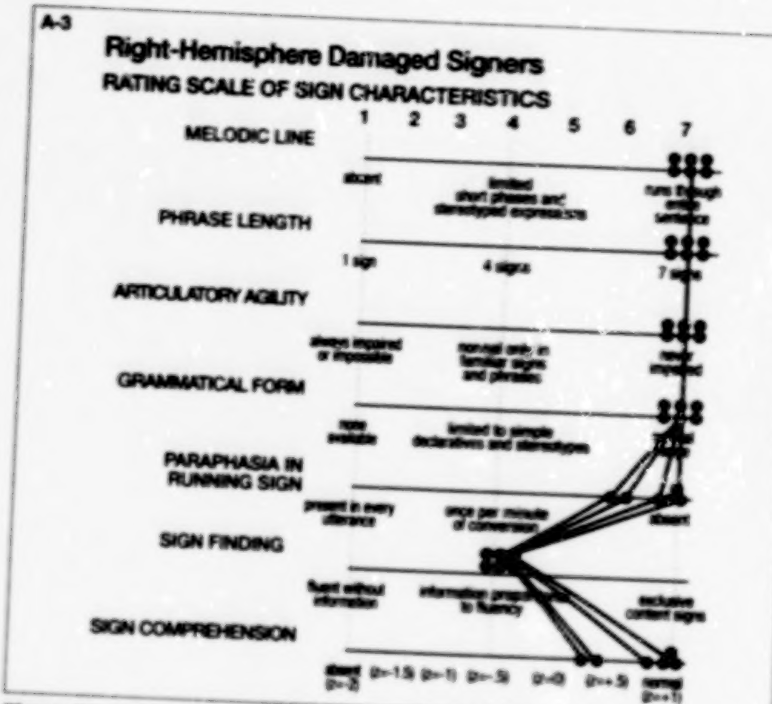


Figure 2A. Sign profiles of left-lesioned signers (A-1), right-lesioned signers (A-3), and the control group (A-2).

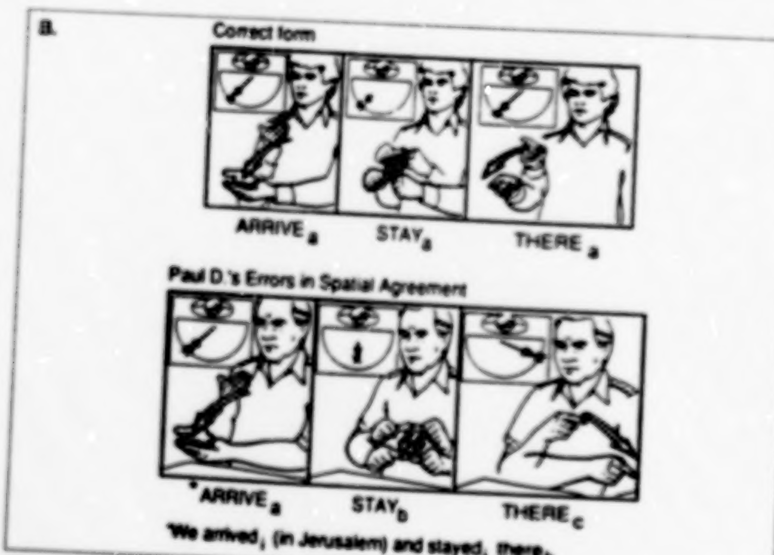


Figure 2B. Impairment in spatially organized syntax in left-lesioned signers.

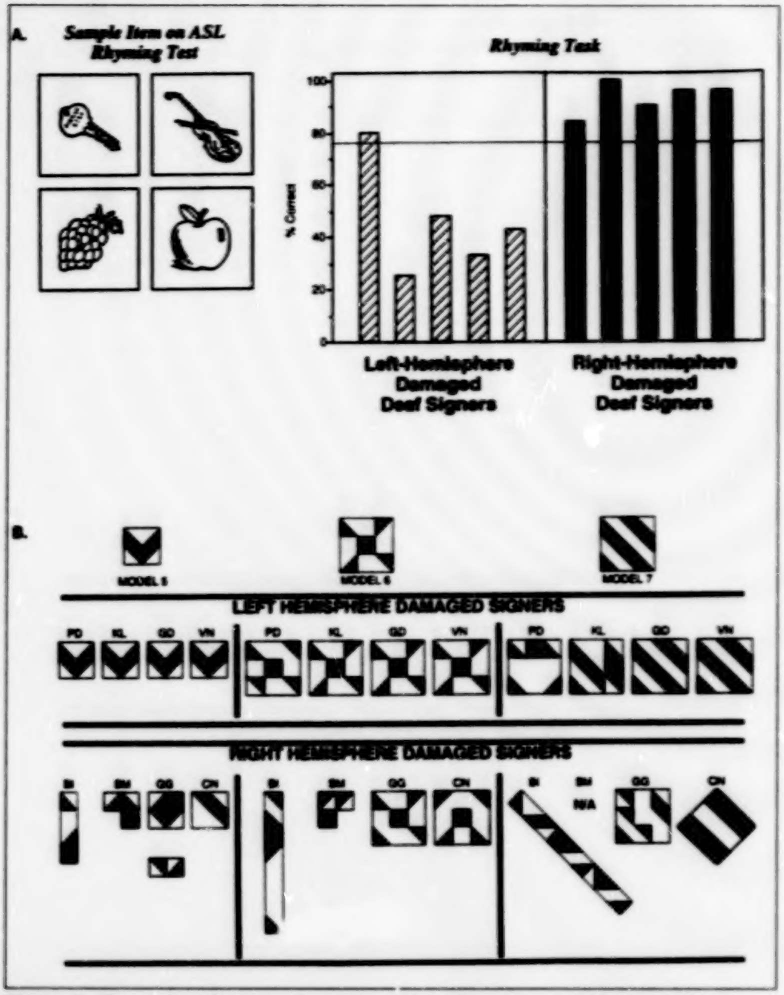


Figure 3. The contrast between language and nonlanguage spatial processing in left- and right-lesioned signers. (A) Phonological processing is impaired in LHD but not RHD. (B) Block design is impaired in RHD but not LHD.

Left-Hemisphere Lesions and Sign Language Grammar

Our first major finding is that only deaf signers with damage to the left hemisphere show sign language aphasias. Marked impairment in sign language after left-hemisphere lesions was found in the majority of the left-hemisphere damaged (LHD) signers but not in any of the right-hemisphere damaged (RHD) signers, whose language profiles were much like matched controls. Figure 2A pre-

sents a comparison of LHD, RHD, and normal control profiles of sign characteristics from our Sign Diagnostic Aphasia Examination—a measure of sign aphasia. The RHD signers showed no impairment in any aspect of ASL grammar; their signing was rich, complex, and without deficit, even in the spatial organization underlying sentences of ASL. By contrast, signers with LHD showed markedly contrasting profiles: one was agrammatic after her stroke, another made frequent paraphasias at the sign internal level, and a third showed grammatical paraphasias, particularly in morphology. A fourth deaf signer showed deficits in the capacity to perform the spatially encoded grammatical operations which link signs in sentences, a remarkable failure in the spatially organized syntax of the language (figure 2B). In contrast, none of the RHD signers showed any within-sentence deficits; they were completely unimpaired in sign sentences and not one showed any hint of aphasia for sign language (in contrast, however, to their marked nonlanguage spatial deficits, described below).

Moreover, we find dramatic differences in performance between left- and right-hemisphere damaged signers on formal experimental probes of sign competence. For example, we developed a test of the equivalent of rhyming in ASL, a probe of phonological processing. Two signs "rhyme" if they are similar in all but one phonological parametric value such as handshape, location, or movement. To tap this aspect of phonological processing, subjects are presented with an array of pictured objects and asked to pick out the two objects with signs that rhyme (figure 3A). Left-hemisphere damaged signers are significantly impaired relative to RHD signers and controls on this test, another sign of the marked difference in effects of right and left hemisphere lesions on signing. On other tests of ASL processing at different structural levels, we found similar distinctions between left- and right-lesioned signers, with the right-lesioned signers much like the controls, but the signers with left-hemisphere lesions significantly impaired.

Right-Hemisphere Lesions and Spatial Processing

These results from language testing contrast sharply with results on tests of nonlanguage spatial cognition. The RHD signers are significantly more impaired on a wide range of spatial cognitive tasks than LHD signers, who show little impairment. Drawings of many of the RHD signers (but not those with LHD) show severe spatial distortions, neglect of the left side of space, and lack of perspective. Figure 3B presents samples of RHD versus LHD signers' performance on a

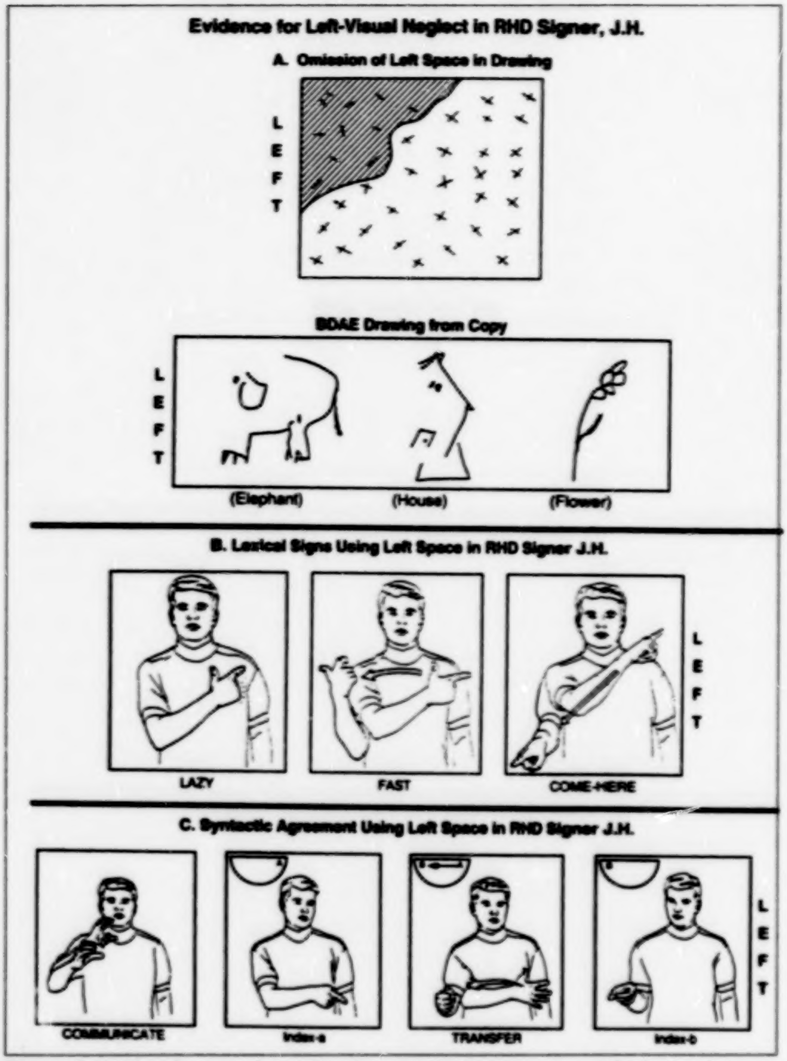


Figure 4. Neglect for spatial cognition but not sign language in a right-lesioned signer.

block design task. Note the RHD signers' tendencies to break the overall configuration of the design in the block design task and their spatial disorganization, compared to LHD. Yet, astonishingly, these sometimes severe spatial deficits among RHD signers do not affect their competence in a spatially nested language, ASL.

The finding that sign aphasia follows left-hemisphere lesions but not right-hemisphere lesions provides a strong case for a

modality-independent *linguistic* basis for the left-hemisphere specialization for language. These data suggest the left hemisphere is biologically predisposed for language itself, independent of language modality. Thus, hearing and speech are not necessary for the development of hemisphere specialization—sound is not crucial. Furthermore, the finding of a dissociation between competence in a spatial language and competence in nonlinguistic spatial cognition demonstrates that the type of information encoded in a signal (i.e., linguistic vs. spatial information) rather than the nature of the signal itself (i.e., spatial vs. temporal) determines the organization of the brain for higher cognitive functions.

Sign Language has been found to be preserved in right-lesioned signers. Signers with right hemisphere damage present special issues, since they often show nonlanguage spatial deficits. Several right-lesioned signers have severe left hemispatial neglect—that is, selective inattention to the left side of space, which is apparent in drawings, where the left side is frequently omitted. Or, in a task where they are asked to cross out all the lines on a page, they characteristically omit several lines on the left side of space (figure 4). The left-field neglect shows up on almost all visual tasks. Such a distortion in spatial cognitive abilities might certainly be expected to impact processing and production of a visual spatial language. Remarkably, this does not have an impact on signing or on the ability to understand signing, which is unimpaired. Inattention to the left portion of the visual field ***does not hold*** for linguistic stimuli.

In one experiment, we contrasted presentation of signs with presentation of objects to both visual fields. The sign trials used bimanual signs which have one meaning if information from both hands is processed but have a different meaning if information from only one hand is taken into account. The object trials involved simultaneous presentation of different objects in the two visual fields presented in the same spatial relations as the signs. The subject was nearly perfect on the sign identification task, but only half of the object trials were correctly identified, with all the errors involving omission of the object in left hemispace. This pattern of left hemispace omission was not observed in the sign trials. Moreover, although the drawings show left neglect, the subject used the left side as well as the right in producing signs and even used the left side of signing space for establishing nominals and verb agreement appropriately in sign language syntax (figure 4). These results show what little effect right hemisphere damage can have on core linguistic functions, even when the language is essentially visuospatial.

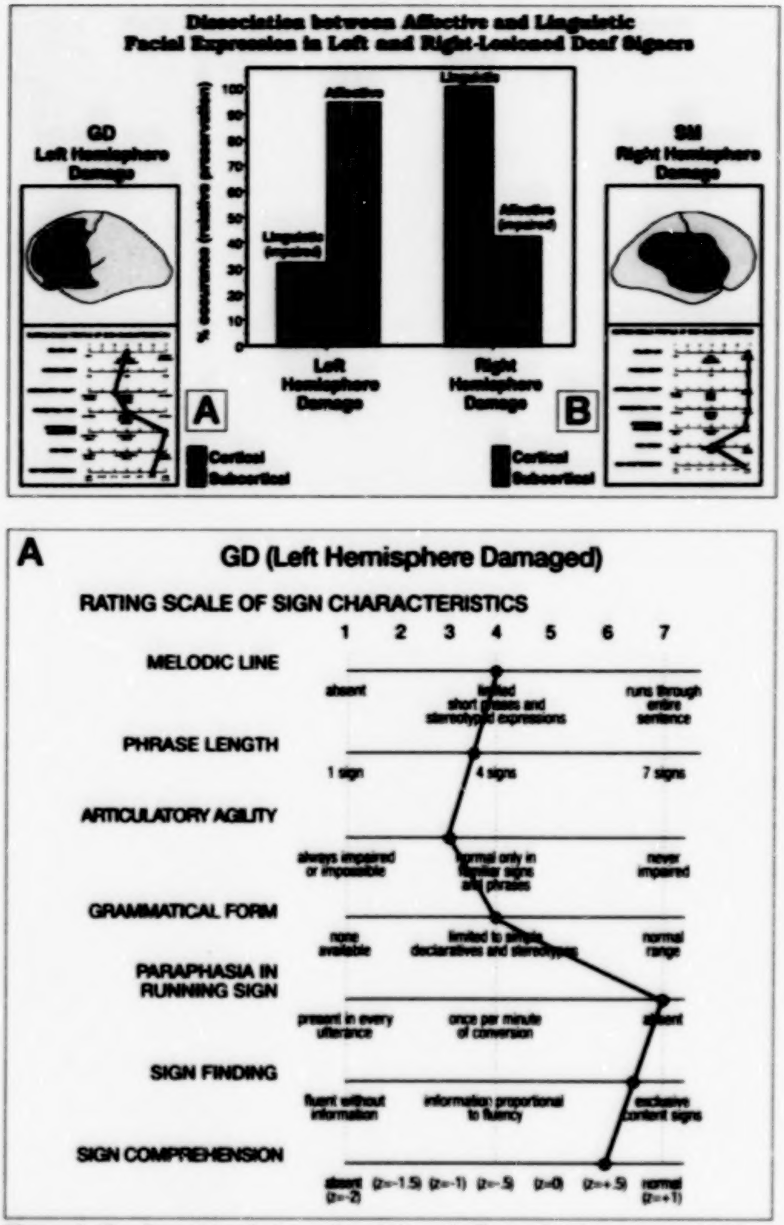
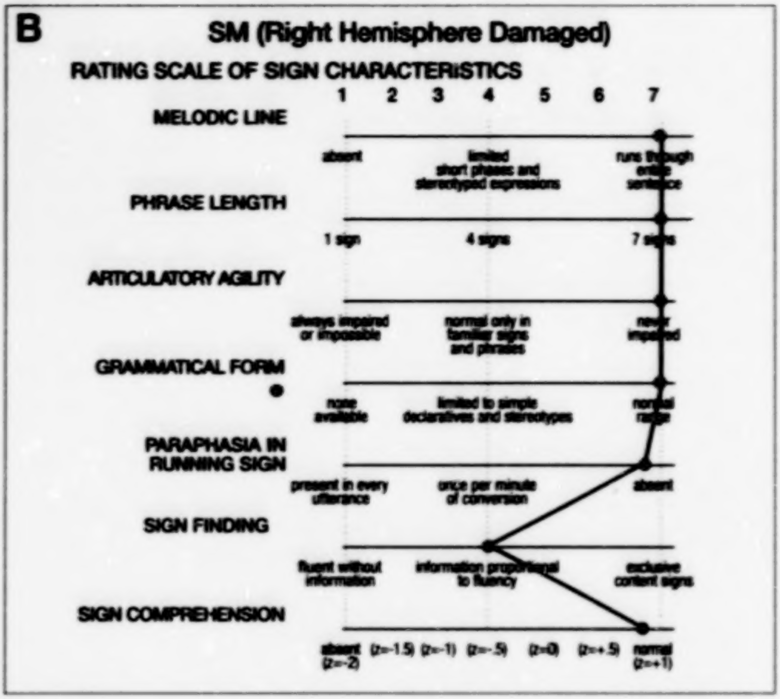


Figure 5. The dissociation between linguistic and affective facial expression in left- and right-lesioned deaf signers.



The Separation between Sign Aphasia and Apraxia

In a long-standing controversy over the nature of aphasic disorders, certain investigators have proposed a common underlying basis for disorders of gesture and disorders of language. One position is that disorders of language occur as a result of more primary disorders of movement control (apraxia). A second position is that both apraxia and aphasia result from an underlying deficit in the capacity to express and comprehend symbols. Since gesture and linguistic symbols are transmitted in the same modality in sign language, the breakdown of the two can be compared directly. In addition to an array of language tests, a series of apraxia tests was administered to brain-damaged deaf subjects, including tests of production and imitation of representational and nonrepresentational movements. The right-hemisphere damaged signers were neither aphasic nor apraxic.

Some strong dissociations emerged, however, between the language and nonlanguage gesture and motor capacities of the left-hemisphere damaged signers, most of whom were aphasic for sign language. The language deficits of these signers, on the whole,

were related to specific linguistic components of sign language rather than to an underlying motor disorder. Nor were their language deficits related to an underlying disorder in the capacity to express and comprehend symbols of any kind. Indeed, we found a dissociation in a left-lesioned signer in the expression and the recognition of signs (which were impaired) contrasted with the expression and the recognition of symbolic gestures and mime (which were preserved).

Converging evidence comes from a study of signers and nonsigners without brain damage in which we compared lateralization for three different types of gestures: signs of ASL, symbolic gestures that are not part of a linguistic system, and arbitrary nonlinguistic gestures. Our results indicate left-hemisphere specialization for both sign and speech in hearing signers, and for sign in deaf signers, but not for arbitrary or symbolic gestures in either group. Thus, we find distinctions between motoric, symbolic, and linguistic communication in signers.

Affective and Linguistic Facial Expressions

Investigation of brain organization for sign language has focused primarily on the manual signs. However, there is another layer of structure of sign language that can afford special clues to the basis of hemispheric specialization, namely facial expressions. In ASL, facial signals function in two distinct ways: (1) Specific facial expressions have arisen as a part of the grammar, co-occurring with manual signs, and are used to signal grammatical constructions such as relative clauses, conditionals, topics, and so forth, and (2) for signers facial expressions can convey affective information just as facial expressions typically do with hearing non-signers.

Generally, studies of hearing subjects have shown that affective facial expression is mediated by the right hemisphere, but our research with deaf signers suggests that not all facial expressions are treated alike by the brain. Interestingly, we have found dissociations between left- and right-lesioned signers in terms of production of the two different functions of facial expressions. A right-lesioned signer was far more likely to produce linguistic facial expressions where required but showed a clear tendency to omit affective facial expression where expected. In contrast, two left-lesioned signers, who are aphasic for sign language but still produce complex ASL sentences, showed precisely the opposite effect, with full use of affective facial expression present throughout, but with frequent omissions of linguistic facial expressions where required

frequent omissions of linguistic facial expressions where required (figure 5).

These are important findings, since presumably one and the same muscular system is involved. Thus, one cannot account for the findings in terms of weakness of facial muscles but rather must account for them in terms of dissociation between linguistic and affective facial expressions. Like the processing of spatial relations, the brain basis for processing facial signals appears highly dependent on the type of information encoded in the signal. Linguistic facial signals are mediated by the left hemisphere, whereas affective facial signals are mediated by the right hemisphere in these deaf signers.

These results show that linguistic information and nonlinguistic information are mediated in qualitatively distinct ways in the brains of deaf signers. Not only does this cleavage show up in processing linguistic versus nonlinguistic spatial relations but also in perceptual attention and production of two different classes of facial expressions.

Spatial Syntax versus Spatial Mapping in ASL

Until now, we have considered the spatial organization underlying grammatical contrasts, most notably syntax, in ASL. That is, ASL uses spatial relations to encode syntactic information such as grammatical subjects and objects of verbs, through manipulation of arbitrary loci and relations among loci in a plane of signing space. As opposed to its syntactic use, space in ASL functions in a topographic way. The same plane of signing space also may be used in spatial mapping; that is, the space within which signs are articulated can be used to describe the layout of objects in space. In such mapping, spatial relations among signs correspond topographically to actual spatial relations among the objects described, as opposed to representing arbitrary grammatical information. We investigate the breakdown of two uses of space within sign language, one for spatially organized syntax and the other for directly representing spatial relations in ASL. Right- and left-lesioned deaf signers provide striking dissociations between processing spatial syntax versus spatial mapping. These subjects were given tests designed to probe their competence in ASL spatial syntax and spatial topographic processing. The combined results on the spatial syntax tests reveal significant differences between the two groups: left-lesioned signers were significantly impaired on syntax tests, but right-lesioned signers' performance was not distinguishable from normal controls. Contrastingly, on the tests of spatial topographic processing, right-

Figure 6. RHD lesion reconstructed by Brainvox (Damasio and Frank, 1992, courtesy of A. and H. Damasio).

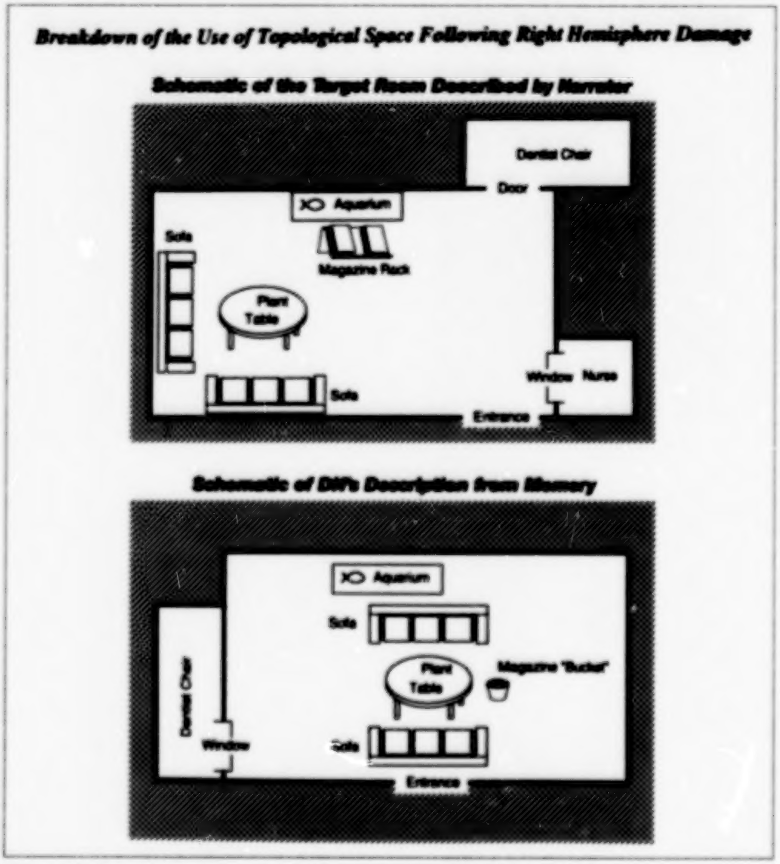


Figure 7. Disorganization in spatial mapping in right-lesioned signer.

lesioned signers revealed significant deficits, whereas left-lesioned signers performed well.

A powerful example of the dissociability of spatial syntax from spatial mapping comes from a RHD signer. The lesion of this subject involves the right superior parietal cortex with medial extension to the corpus callosum. This is illustrated in a three-dimensional reconstruction from in vivo MRI images using Brainvox, a system developed by Damasio and Frank (figure 6). Like other right-lesioned signers, the subject is not aphasic. Her processing on ASL grammar tests was nearly perfect, and her use of spatially organized syntax is error free. When she was asked, however, to repeat short stories in ASL that involved spatial descriptions—stories describing the layout of a particular dentist's office, for example—the description was impaired severely. This right-lesioned signer does quite well in remembering and reproducing the actual items within a description (unlike some of our normal controls), but she completely fails in placing these objects in correct spatial locations in the signed story. Control subjects correctly located nearly all the items remembered from the story, whereas our subject correctly located only about a third of the items remembered. The reconstructed layout of the signed description of a dentist's office is illustrated in comparison to the ASL description in the experiment in figure 7. This signed description shows a marked spatial disorganization of elements within the room; the subject incorrectly specified the orientation and locations of items of furniture but tended to lump all of the furniture in the center of the room, thus showing marked impairment in spatial mapping in ASL. Thus, even within signing, the use of space to represent *syntactic* relations and the use of space to represent *spatial* relations may be differentially affected by brain damage, with the syntactic relations disrupted by left-hemisphere damage and the spatial relations disrupted by right-hemisphere damage.

Converging Evidence about Brain Organization for ASL

A recent study by Damasio et al. analyzed the sign language of a hearing signer proficient in ASL during a left intracarotid injection of sodium amytal (WADA Test), and before and after a right temporal lobectomy for her epilepsy. Neuropsychological and anatomical asymmetries suggested left cerebral dominance for auditory-based language. Single photon emission tomography revealed lateralized activity of the left Broca's and Wernicke's areas for spoken language (figure 8). The WADA Test, during which all left lan-

Figure 8. Single photon emission tomography reveals activity of the left Broca's and Wernicke's areas.

Figure 9. The conflict between Sign and speech errors during left WADA Test. (From *Nature*, reprinted with permission in TINS, courtesy of A. Damasio.)

Figure 10. After surgery, English and sign language abilities are intact.

guage areas were rendered inoperative, caused a marked aphasia in both English and ASL. The patient's signing was markedly impaired, with many incorrect sign responses and sign neologisms. Interestingly, since she was hearing and could sign and speak at the same time, it was possible to compare her responses in two languages simultaneously—a unique possibility for languages in different modalities. This result revealed a frequent mismatch between word and sign, the sign being frequently incorrect both in meaning and in form (figure 9). Subsequently, the patient had the anterior portion of her right temporal lobe surgically removed (figure 10). Analysis of her language after the surgery revealed no impairment of either English or sign language. These findings further support the notion that the left cerebral hemisphere subserves language in a visuospatial as well as an auditory mode.

Techniques using cortical stimulation mapping and single-unit recording in a hearing signer, in a collaborative study with Ojemann, provide converging evidence. This approach allows us to contrast spoken and signed language neural systems within the same individual. During a left frontotemporoparietal craniotomy under local anesthesia, the subject was tested for both language modalities. The results showed some sites which differentiated sign from spoken word naming and comprehension. Single unit activity also was recorded, results suggesting that in this individual some sites representing sign versus word may turn out to be *different within* the left hemisphere. These converging results, taken together, provide strong evidence for the linguistic specificity of left-hemisphere specialization for language. The evidence so far does *not* suggest that the neural systems subserving the two languages will turn out to be precisely the same.

We are investigating differences as well as similarities between the neural systems subserving signed versus spoken language. Our growing database of deaf and hearing signers, combined with powerful new techniques in brain imaging, allows us to explore *within* the cerebral hemisphere neural systems subserving signed and spoken language. We now are beginning to amass evidence that suggests both some central commonalties and some peripheral differences between the neural systems underlying signed and spoken languages. Patterns of language breakdown and preservation in left- as opposed to right-lesioned signers lead us to the following conclusions: Because the left-lesioned signers show frank sign language aphasias and the right-lesioned signers show preserved language function, it appears that the left cerebral hemisphere is specialized for sign language. Thus, neural systems within

the left hemisphere emerge as special-purpose linguistic processors in individuals with profound and lifelong auditory deprivation and who communicate with linguistic systems that use radically different channels of reception and transmission from that of speech. In this crucial respect, brain organization for language in deaf signers parallels that in hearing, speaking individuals.

Our data further suggest that differential damage within the left hemisphere produces different forms of sign language aphasia. We are working on the possibility that anatomical structures within the left hemisphere that subserve visual-gestural language differ in part from those that subserve auditory-vocal language. We now are mapping out the differences between spoken and signed language neural systems within the left hemisphere which may arise from the nature of the different visual input pathways and manual output pathways. Several left-lesioned signers exhibit sign language aphasias from lesions to systems that would not be expected to lead to language disruption in spoken language.

Language, Modality, and the Brain

Nonetheless, the similarities between signed and spoken language in interhemispheric organization are most revealing. These studies of language in a different modality show that the left cerebral hemisphere in humans is specialized for signed as well as spoken languages. Not only does this finding provide a striking example of neuronal plasticity, but it also suggests an innate biological basis for that unique human capacity: language.

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Suggested Readings

Bellugi, U. 1980. The structuring of language: Clues from the similarities between signed and spoken language. In *Signed and Spoken Language: Biological Constraints on Linguistic Form*, ed. U. Bellugi and M. Studdert-Kennedy, 115–40. Dahlem Konferenzen. Weinheim/Deerfield Beach, Florida: Verlag Chemie.

Bellugi, U., H. Poizner, and E.S. Klima. 1989. Language, modality and the brain. *Trends in Neurosciences* 10:380–88.

Bellugi, U., H. Poizner, and E.S. Klima. 1990. Mapping brain function for language: Evidence from sign language. In *Signal and Sense: Local and Global Order in Perceptual Maps*, ed. G.M. Edelman, W.E. Gall, and W.M. Cowan, 521–43. New York: Wiley-Liss.

Corina, D., H. Poizner, U. Bellugi, T. Feinberg, D. Dowd, and L. O'Grady-Batch. 1992. Dissociation between linguistic and nonlinguistic gestural systems: A case for compositionality. *Brain and Language* 43, no.3:414–47.

Damasio, A., U. Bellugi, H. Damasio, H. Poizner, and J. Van Gilder. 1986. Sign language aphasia during left hemisphere amytal injection. *Nature* 322:363–65.

Damasio, H., and A.R. Damasio. 1989. *Lesion Analysis in Neuropsychology*. New York: Oxford University Press.

Damasio, H., and R. Frank. 1992. Three-dimensional in vivo mapping of brain lesions in humans. *Archives of Neurology* 49:137–43.

Emmorey, K., S.M. Kosslyn, and U. Bellugi. 1993. Visual imagery and visual-spatial language: Enhanced imagery abilities in deaf and hearing ASL signers. *Cognition* 46:139–81.

Klima, E.S., and U. Bellugi. 1979. *The Signs of Language*. Cambridge, Mass.: Harvard University Press. (Paperback reprint, 1988.)

Poizner, H., E.S. Klima, and U. Bellugi. 1987. *What the Hands Reveal about the Brain*. Cambridge, Mass.: MIT Press/Bradford Books. (Paperback reprint, 1990. German translation: *Was die Hande uber das Gehirn Verraten*, Hamburg: Signum-Verlag, 1990; Japanese translation, Tokyo: Shinyosha Press, in press.)

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FUNCTIONAL NEUROIMAGING IN BRAIN AREAS INVOLVED IN LANGUAGE

Steven E. Petersen

The ability to communicate with other people through language is one that distinguishes humans from other animals, and for this reason, language has been the object of study for investigative disciplines ranging from neurobiology to philosophy. One focus of study has been how the structure and function of the brain act as a substrate for language. An understanding of how the brain underlies language will not only satisfy curiosity about ourselves but will also offer insights into medical problems affecting communication between people. Examples of such medical problems include brain damage following strokes, degenerative diseases like Alzheimer's dementia, and mental illness like schizophrenia.

Most of our understanding of how the brain underlies language comes from careful behavioral studies in normal people and people with brain damage (most often from stroke). In the past decade, the development of functional neuroimaging technologies has allowed scientists to obtain views of the normal human brain at work. Functional neuroimaging technologies include positron emission tomography (PET), functional magnetic resonance imaging (fMRI), and magneto- and electro-encephalography (MEG, EEG). All of these techniques attempt to relate a measurement of brain physiology to a scientific task a person is performing. This chapter will focus attention on measurements using PET while people perform various tasks (in this case, very simple tasks) using single words and objects that are very similar to words.

PET Methods

A large doughnut-shaped instrument called a PET scanner, or PET camera, produces pictures of how positron-emitting radiation is distributed in the scanner opening—or hole of the doughnut—

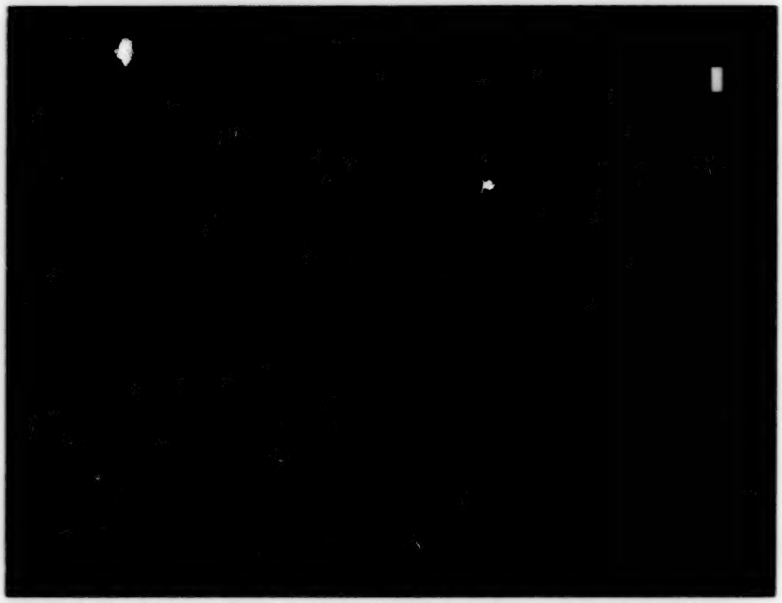

Figure 1. The first row shows seven horizontal slices from a scan when subjects responded with a verb to a visually presented noun. The second row shows the same slices taken from the same subject when the subject simply says the noun that is presented. The third row shows the same slices of the subtraction scan (the areas that are different) between the two conditions. For these scans the nose is up, and the back of the head is to the bottom. The hotter colors (red and white) are present where there are areas of high change, the cooler colors where there is little change. The bottom row of images is the average of several individuals doing these same tasks. Notice that the signal stands out more clearly from the background.

and any substance that can be tagged with a positron-emitting radioactive substance can be measured in these pictures.

Specific PET methods include the following steps:

(1) *Application of Oxygen-15-labeled water as a blood flow tracer.* Oxygen-15-labeled water involves a small number of the oxygen molecules in H_2O that have been changed to Oxygen 15, a positron emitter. The reason for using this tracer is that the areas of the brain that are "working harder" during the performance of a certain task will have higher blood flow and metabolism, just as a working muscle has higher blood flow and metabolism. Oxygen-15 labeled water acts as a tracer of blood flow when injected into the bloodstream just before a PET scan. For monitoring brain blood flow, the top of a person's head is placed in the central opening of the scanner. By measuring the distribution of the labeled water while people perform carefully chosen tasks, a picture can be made

of those parts of the brain that are working the hardest. The hard-working areas presumably are involved in the performance of the task. Because Oxygen-15 has a short half-life of about two minutes, the investigator can make eight to ten measurements in a single individual in a single session. This opportunity to make multiple scans leads to step 2.

(2) *Making pictures of the changes between blood flow measurements by creating subtraction images.* To see the areas activated by a particular visual stimulus, we have someone view a blank screen in one scan and the same screen with the stimulus on it in another scan. By subtracting the first scan from the second, the areas that are changed by the addition of the stimulus are shown (figure 1).

(3) *Averaging the pictures across a number of individuals.* As is the case in many scientific studies, a single measurement is not as accurate or reliable as making several measurements and averaging them. Techniques have been developed to allow the averaging of PET subtraction images across individuals and to see the areas commonly changed across the group of subjects (figure 1).

(4) *Application of statistical techniques and computer routines to localize the areas of change in the brains, and determine if they are statistically reliable.* These techniques have been applied to the two experiments described below to describe how people process single words presented to their eyes and ears.

Experiment 1

For experiment 1, the activity in the brain engendered by the simple presentation of words to the eyes and ears was compared. Three conditions were presented to the people in the scanner. The control condition involved individuals looking at a cross hairs on a computer screen (a small "+" sign) while holding their eyes still. This condition was subtracted from two active conditions where words were presented to the subjects. In both active conditions, the subjects also were instructed to hold their eyes still on the cross hairs, or plus sign. In one of the active conditions, subjects were presented words briefly (about 0.15 seconds) on the screen, just below the plus sign. Every second a new word was presented on the screen in this *visual words* condition. For the second active scan, rather than having the words appear on the screen, the words were presented through tiny speakers placed in the ears like hearing aids. Again, a new word was presented every second, and this condition was called *auditory words.*

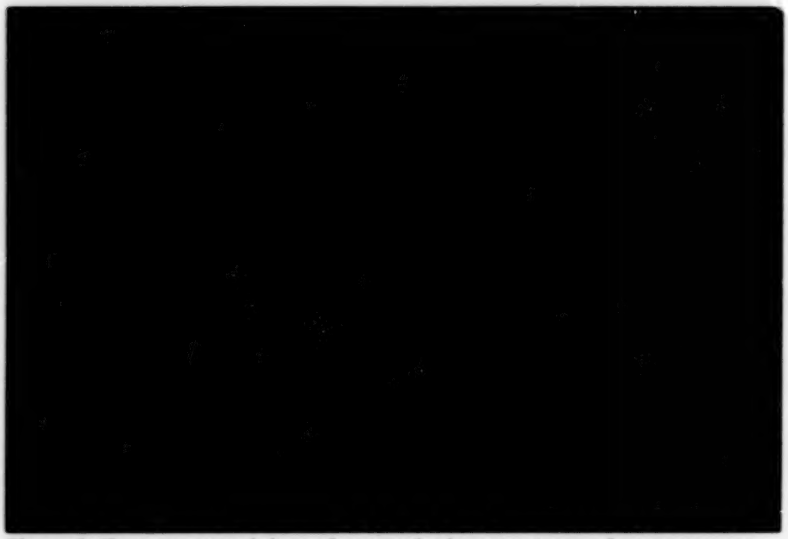

Figure 2. These are sagittal slices of averaged subtraction images for experiment 1. Sagittal slices are taken as if you view the brain from the side with the intervening tissue removed so that you can see inside. The front of the brain is placed to the left and the back of the brain to the right. All of the slices are from the left side (hemisphere) of the brain. The two slices on the left are from subtractions when words are presented visually, the right slices when words are presented to the ears. The top two slices are taken about an inch from the center of the head and show in the back of the brain clear activation when words are presented visually, but no activation when words are presented auditorily. The opposite is true in the bottom row where the slices are taken further from the center of the brain (about 2 inches).

The pictures shown in figure 2 are sagittal slices through the PET scan images. A sagittal slice is a side view of the brain, and in the case of these slices, they are taken so that the front of the head is to the left. The slices in the two rows are taken at different distances from the center of the head. As can be seen in figure 2, different areas are activated by visual and auditory words. The top two slices were taken approximately 2.5 cm (about an inch) to the left of the center of the head. These slices show a clear activation in the back of the head for visual presentation of words, but little or no activation for the auditory words. When moving another inch to the left so the slice is taken further from the center of the head, one sees activation for auditory words but not visual words. No part of the brain appears to be activated by both visual and auditory words when presented in this simple, passive way.

The general location of these responses is not a big surprise. Scientists have known for some time that early visual processing

takes place in the cortex in the occipital lobe at the back of the head, whereas early auditory processing takes place more toward the front of the brain and further away from the midline in the temporal lobes. The visual response shown in figure 3 is probably a part of the visual cortex known as visual extrastriate cortex.

This first experiment leaves several questions unanswered. For example, one could ask whether the visual response results from the processing of the lines, curves, and corners that are present in the letters, whether, in other words, the activation is triggered by the simple visual features of the stimuli in the visual words condition. On the other hand, the activation could result from processing at a higher level, such as the level of letters, the first level of analysis special to words. Or finally, actual recognition or processing of the items as words or at some intermediate level between words and letters, such as the level of orthographic regularity, may cause activation of these parts of the brain.

Orthographic regularity is the property of following the spelling rules of a language, in this case English. Strings of letters that follow the spelling rules but are not real words can be produced, and these are called pseudowords. An example of this is "toglo." A person could read this pseudoword aloud but recognize that in his or her experience "toglo" is not a real word. This intermediate level of processing is important because several behavioral experiments have shown that at the earliest stages of visual processing real words and pseudowords are processed similarly, whereas simple strings of letters are processed differently. The brain might make an early judgment about whether a collection of letters might be a word candidate or not, based on spelling regularity. If a string of letters is regular, further processing might take place, for instance to "look up" its meaning.

Experiment 2

The second experiment focuses on the issues raised by the first experiment about the relation of the activation in the extrastriate visual cortex to the presentation of visual words. As in the first experiment, the control condition that was subtracted from all of the active scans was the presentation of a plus sign with the instruction to hold the eyes still for the duration of the scan. In this case there were four active scan conditions during which visual stimuli were presented. Each of the four active scans presented different types of visual stimuli.

For one scan, visual words again were presented to see whether results from the first experiment would replicate under

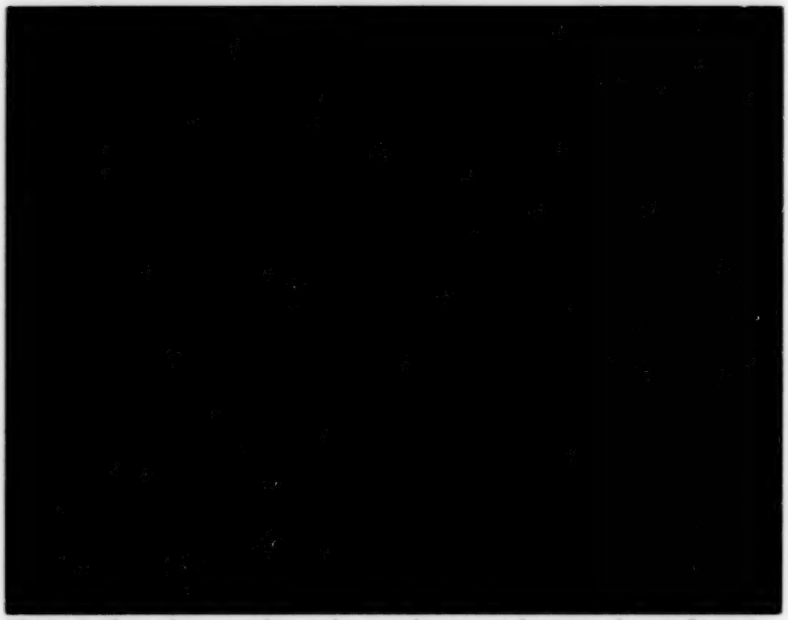

Figure 3. These slices are taken at the same location as the upper slices in figure 2. Clear activation is seen near the base of the cortex for the real words and pseudoword conditions, with little or no activation for the letter strings condition, and lesser activation placed higher up in the brain for the false font condition.

these slightly different conditions, and this was called the *real words* condition. In another scan, a series of stimuli were computer generated to have all of the visual features of letters (e.g., the same number of curved and straight lines, the same amount of light, and so on), without actually forming letters. These stimuli looked something like hieroglyphics but were clearly not letters, and this was called the *false font* condition. The third scan, the *letter strings* condition, presented a series of random letter strings like JVTVC. Finally, a series of letter strings that followed the spelling rules of English, but were not real words, were presented in the *pseudowords* condition.

The reasoning behind this experiment was the following. If the activation at the extrastriate region shown in figure 2 results from processing at the level of the visual features of the stimuli, then activity should be present for all of the active conditions, since the same visual features are present in all of the stimulus sets. If the activation is related to processing at the level of letters, there should be activation for words, pseudowords, and letter strings but no activation for the false font condition. If activation is related to process-

ing at the level of words themselves, activation would be expected only in the real words condition. If, however, activation is related to processing at the level of orthographic regularity, there should be activation for the pseudowords and real words but not for the other two stimulus sets.

As can be seen in figure 3, this final alternative, processing at the level of orthographic regularity, appears to be true for this region of extrastriate cortex. The region pictured appears to be processing at the level of orthographic regularity. Little or no activation appears near the bottom of the cortex for false fonts and letter strings, but clear and extensive activation is visible for the pseudoword and real word conditions. This distinction is interesting because, although this region is early in the stream of visual processing, it is making the subtle distinction between strings of letters that could be words and those that could not be words based on their spelling regularity. Furthermore, this distinction is one that must be "wired up" long after birth as a person learns how to read.

Further evidence that this extrastriate cortical region is important for reading comes from studies of people who have damage to this part of the brain. They often show a syndrome called pure alexia, a difficulty in reading but with the rest of their language abilities intact. Pure alexics sometimes show an ability to read letter by letter. Letter-by-letter reading is consistent with the existence of a processing region in the back of the brain encoding letter strings above the level of the single letter, perhaps at the level of orthographic regularity.

Conclusions

One of the major interests in neuroscience is to begin to understand the function of the brain well enough so that we might gain some insight into our understanding of ourselves. In trying to understand the neural underpinnings of language, we are making the first tentative steps in that direction. A clear and detailed understanding of this complex problem is far into the future, but several tools, including functional neuroimaging, are available to help us find our way. As our knowledge about how the brain "does" language increases, insights into how the disordered brain is deficient in this important human ability will be sharpened, and new ways of dealing with disorders may be discovered. These possibilities make the Decade of the Brain an exciting time in which to study the neuroscience of complex behaviors like language.

I would like to acknowledge my collaborators in this research, including Marc Raichle, Peter Fox, Mark Mintun, Mike Posner, and Avi Snyder, and all of the other people who made this work

possible. This work was done with funding from the National Institute of Neurological Diseases and Stroke and the McDonnell Center for the Study of Higher Brain Function.

Suggested Readings

Carr, T.H., and A. Pollatsek. 1985. Recognizing printed words: A look at current models. In *Reading Research* ed. D. Besner, T.G. Weller, and G.E. MacKinnon, 2–73. New York: Academic Press.

Damasio, A. 1992. Aphasia. *New England Journal of Medicine* 326:531–39.

Petersen, S.E. and J.A. Fiez. 1993. The processing of single words studied with positron emission tomography. *Annual Review of Neuroscience* 16:509-30.

Petersen, S.E., P.T. Fox, A.Z. Snyder, and M.E. Raichle. 1990. Activation of extrastriate and frontal cortical areas by visual words and word-like stimuli. *Science* 249:1041–44.

INVESTIGATING LANGUAGE DURING AWAKE NEUROSURGERY

George A. Ojemann

Certain neurosurgical operations for the treatment of epilepsy provide unique opportunities to investigate the brain organization of language. In these operations, the patient is awake for a portion of the procedure when the brain is exposed. This approach permits the use of electrical activity recorded from the brain surface to identify tissue to be removed to treat the epilepsy and the identification of functionally important areas of the brain to be spared in that removal. General anesthesia interferes with these measures. Because the brain has no sensors to detect either touch or pain, patients can be awake and reasonably comfortable during that part of these operations when the brain is exposed. With modern short-acting anesthetic agents, the patient can be asleep during parts of the procedure that might be uncomfortable or noisy (for instance, local anesthetics can be used to block sensation in pain-sensitive structures such as the scalp and dura during the craniotomy) and then awakened.

Usually these awake operations provide access to a portion of only one cerebral hemisphere in a patient. Consequently they are primarily of value in addressing issues of intrahemispheric language organization. Investigating that issue in the context of these awake operations began with the studies of Wilder Penfield at the Montreal Neurological Institute a half century ago.

Reviewed here are some more recent investigations of language function in this setting by the author and his colleagues at the University of Washington. Four different techniques have been used in these investigations, each providing a different perspective on where and how the brain generates language. In essence, these studies show that separate systems exist with differing localized areas for many discrete functions of language.

Several techniques are directed at questions of localization. For example, where are nerve cells active during a particular dimension of language? Electrical stimulation mapping, also used in Penfield's studies, is the oldest of these techniques. Here, function in a local area of the brain is blocked by the electrical current while the patient performs a test of some dimension of language. An area of brain is "related" to that language dimension if the patient's performance fails during application of the current to that area. Thus, this technique identifies brain areas that must be functioning for successful execution of a language dimension. I will call these "essential" areas for language.

The study of stroke patients relates a brain area to language in much the same way, by failures in language with loss of function in particular brain structures, although the area of brain inactivated by electrical stimulation mapping is usually much smaller than that effected by brain damage.

We also have investigated language localization with the new technique of optical imaging of the "intrinsic signal." This technique indicates where nerve cells are active, and thus "participating" in a language behavior, but not whether that activity is "essential" for that behavior. The intrinsic signal was first identified in primate visual cortex as subtle changes in the reflection of light from the brain surface in areas of neuronal activity. The exact mechanism is not known but probably involves local increases in blood volume or local glial response, and perhaps also neuronal swelling associated with neuronal activity. Michael Haglund, Daryl Hochman, and I recently reported the first recordings with this technique during language measures in humans.

Other techniques used with these intraoperative investigations raise questions of physiology. What mechanisms are active during a language measure? We have examined changes in the brain waves recorded directly from the brain surface (the electrocorticogram or ECoG) during language measures comparing differences between recordings from essential or nonessential language sites and between the same visual cues used in language or nonlanguage (spatial) tasks. These studies provide insights into mechanisms active at essential language sites. We also have recorded the activity of individual neurons through microelectrodes. These recordings provide a direct measure of what nerve cells are doing during language activity, but because microelectrode recording is invasive, the observations are, of necessity, confined to cortex not essential for language.

These techniques have been applied during measures of a number of different language dimensions. The most extensive ex-

perience is with object naming, and there are several reasons for this. One is historical: Naming was the language measure used in Penfield's original work. Another reason is that naming deficit is a characteristic of all types of language disturbances following brain damage. This makes naming a particularly useful language measure to achieve a practical goal of stimulation mapping, which is to screen the cerebral cortex for a role in language in order to avoid those areas during removal of the epileptic tissue. Indeed, we have shown that when removal of epileptic tissue comes close to a site identified as essential for naming, a postoperative deficit is likely to be revealed by sensitive neuropsychological tests of all aspects of language. This deficit is absent if the removal is not close to a site essential for naming. It is not related to the size of the removal, the preoperative language ability, or the success of the operation in controlling seizures. Here I will review findings on brain organization of language derived from the study of changes in naming.

Electrical Stimulation Mapping

Applying an electrical current to the brain surface has a variety of excitatory and inhibitory effects. Empirically, most excitatory effects are from the primary motor and sensory cortices. Nothing is detected by the patient from stimulation of wide areas of association cortex. If the patient is naming object pictures, however, then stimulation of some of those sites in association cortex where no responses occurred in the quiet patient will now alter naming repeatedly. At some of those sites stimulation blocks all speech; at other sites it provokes errors in naming, but speech is present during stimulation, a change called "anomia." Presumably at these sites the predominant effect of stimulation is the blocking of local function at a site essential for language.

In any one patient, multiple separate sites usually exist where stimulation repeatedly alters naming, as illustrated in figure 1. In many patients, each of these sites has a surface area of from 1 to 2 square centimeters, sometimes with sharp boundaries, but at other sites with a more gradual boundary area where occasional naming errors occur during stimulation. This pattern of multiple separate sites for a function distributed across the association cortex has been identified as a general principal of cortical organization in subhuman primates and appears to apply to language in humans as well.

In both these stimulation mapping studies and with brain damage, essential language areas are most often identified in the areas of brain immediately above or below the Sylvian fissure of

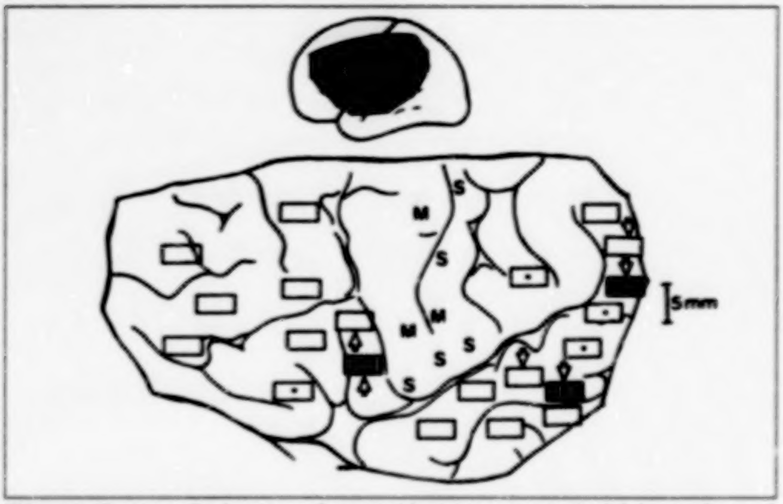

Figure 1. Illustrates the location of essential language areas in the left hemisphere of one patient, based on electrical stimulation mapping during naming. This patient was a twenty-four-year-old female. Squares are sites of bipolar stimulation at 8mA, with 5mm electrode separation, using trains of 1 msec biphasic pulses at 60Hz. Filled or shaded squares are the sites of repeated naming errors that identify essential language sites. Dots are sites of single errors of uncertain significance. Open squares are sites with no errors. Arrows indicate pairs of sites, one essential for language and one within 5mm with no errors, demonstrating the highly localized nature of these essential language areas. M and S are sites of motor and sensory cortex. (From G. Ojemann. 1983.)

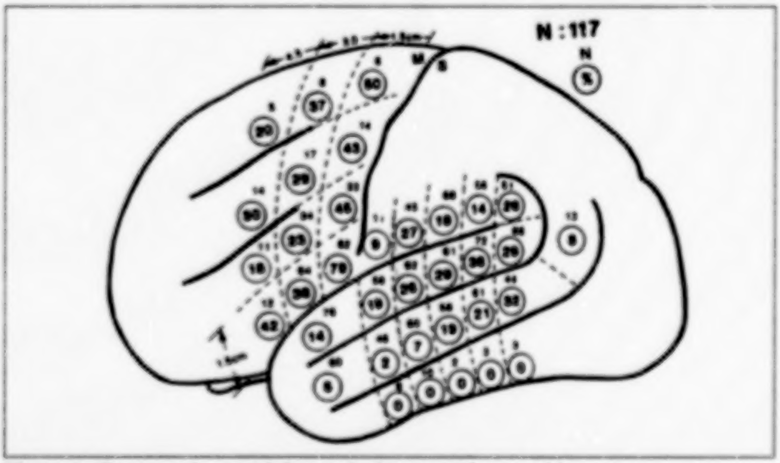

Figure 2. Illustrates the variability in the location of essential language areas in the left hemisphere based on electrical stimulation mapping during naming in 117 patients, all known to be left dominant for language. Dashed lines divide the cortex into zones. In each zone the upper number indicates how many of the patients had a sample in that zone. The lower number in the circle is the percent of that sample with essential language areas in that zone. (From G. Ojemann, E. Lettich, and M. Berger. 1989.)

the language dominant hemisphere, the classical Broca and Wernicke language areas. The most common pattern of stimulation mapping changes is illustrated in figure 1, where one essential site lies within the posterior inferior frontal lobe, and one or more separate sites are localized within the posterior superior temporal lobe.

Some patients with normal language apparently have essential language sites in unusual locations. Jeff Ojemann, Hector Lettich, Mitchel Berger, and I reported on the differences in patterns of essential language areas in 117 patients known to be left-brain dominant. Of those patients who had mapping of both frontal and temporoparietal areas, 17 percent had essential language sites restricted to the frontal lobe, and 15 percent had sites only in temporoparietal lobes. An occasional patient had sites in frontal and parietal but not temporal lobes. In any individual patient, the total surface extent of essential language sites was rather small, usually less than 6 square centimeters, an area substantially less than the total area of the classical Broca and Wernicke language areas. In most patients, essential language sites occupy only a small portion of those areas.

In the 117-patient series, the location of essential language areas showed substantial variability in all lobes as illustrated in figure 2. Only the portion of posterior inferior frontal cortex immediately in front of the face motor cortex demonstrated language sites in over half the patients (79 percent). Only two-thirds of the 117 patients had language sites anywhere in the superior temporal gyrus, although this gyrus is considered part of the classic language cortex and should include Wernicke's area. Those sites in the superior temporal gyrus were distributed throughout its extent. This substantial variability in location of essential language areas suggests that the extent of the classical Broca and Wernicke language areas may be artifacts of averaging measurements for individuals with essential language sites in one corner or another of the traditional areas.

A number of possible explanations could account for the variability. It could reflect an effect of the underlying disease that was the indication for the surgical therapy. This effect is present with diseases acquired in adult life as well as diseases probably related to events in infancy and does not depend on the extent of the epileptic tissue. The variability is related partly to differences in the anatomy of this part of the cerebral cortex, which in itself has substantial variability. The variation in location of essential language sites, however, is greater than this morphologic variability.

Little is known about variability in localization of other functions in the human cortex. If this degree of variability is unique to

language, it suggests that language cortex may be evolutionarily new and not yet settled into a consistent pattern.

In our 117-patient series, different patterns of language localization were related to different patient characteristics. Patterns differed between males and females, with females over-represented in the small group of patients with language sites only in the frontal lobe and overall less likely to have language sites in the parietal lobe. Our finding that on average females may have more extensive frontal language areas and smaller temporoparietal language areas than males is similar to that reported earlier by Doreen Kimura of the University of Western Ontario from the different effects on language of strokes in similar locations in males or females.

Different patterns of language localization also were identified by us for patients with high or low preoperative verbal IQ (VIQ), a measure of overall verbal ability. Patients with essential language sites in superior temporal gyrus were more likely to have lower VIQ's than those with sites in the middle temporal gyrus. These different patterns of language localization apparently have functional consequences, with at least some of the difference in verbal abilities among individuals having a biologic basis.

On the other hand, patterns of localization seem to be little affected by age. Using a somewhat different technology—the technology of chronic intracranial subdural electrodes—we have mapped object-naming in four children four years of age, as well as in several older children. Even the youngest child, age 4 years and 3 days, showed very localized essential language sites, in frontal and temporal lobes, as did our oldest patient, who was 80 years old. Our observations suggest that the size of these sites is not altered with age. The number of sites may increase with age—as the youngest of our patients with multiple separate temporoparietal sites was 8 years old. But this issue is in need of further investigation.

Another feature of these patterns of language localization in need of further investigation is the stability of the patterns over time and after brain damage. We have had occasion to remap adult patients over intervals of a few months without any intervening brain damage and we have found similar patterns. In one case with remapping after several years, however, the pattern was somewhat different. Mapping of patients who have partially recovered from language deficits after brain damage has shown little evidence of sites in unusual "new" locations. Similarly, remapping of patients with increased language deficits from progression of brain tumors has shown only loss of some sites and not the appearance of new

ones. Although essential language sites seem to be in somewhat different locations in different patients, there is presently little evidence of plasticity in their location in an individual patient.

Physiologic Changes in Sites Essential for Naming

In another set of studies, Itzhak Fried and I identified changes in the brain wave activity recorded from the cortical surface that occurred during naming at essential naming sites. The strategy used in these studies was to present the same visual cues, object pictures with stripes across them, in one block with the instruction to name the picture and in another block with the instruction to match the angle of the stripe to a later presented stripe, a task that has been related to function of the nondominant hemisphere. Brain waves were recorded from cortical sites that had the relation to naming independently established by stimulation mapping. With this strategy, brain wave changes during naming could be identified. Some brain wave changes were more prominent at naming sites than in surrounding cortex not essential for naming and were also present at naming sites only, when the same visual cue was used to elicit naming but not the spatial function. These studies were designed to separate any brain wave changes related to motor aspects of speech from changes related to linguistic processes.

We identified two changes in brain wave activity recorded during naming localized to sites essential for naming. At frontal language sites a prominent slow potential appeared shortly after the cue to name and lasted about one second, approximately the time required to name when an overt output was required. At temporal and parietal naming sites the change with the desired characteristics was local desynchronization, loss of activity in the 7–12 Hz (cycles-per-second) frequencies and its replacement by high frequency activity, a change quantitated by spectral density measures and its relation to naming sites during naming established statistically. This change occurred with the same time course as the frontal slow wave, indicating parallel processing at frontal and temporoparietal language sites lasting throughout the language task. The result is in contrast to the classical understanding of language cortex, where language areas were thought to be serially linked with decoding in temporal areas followed by output from frontal areas.

We found no evidence for serial brain wave events, only the events occurring in parallel. Such parallel activation of multiple distributed cortical areas is a general principle of cortical organization in subhuman primates; apparently it also applies to human lan-

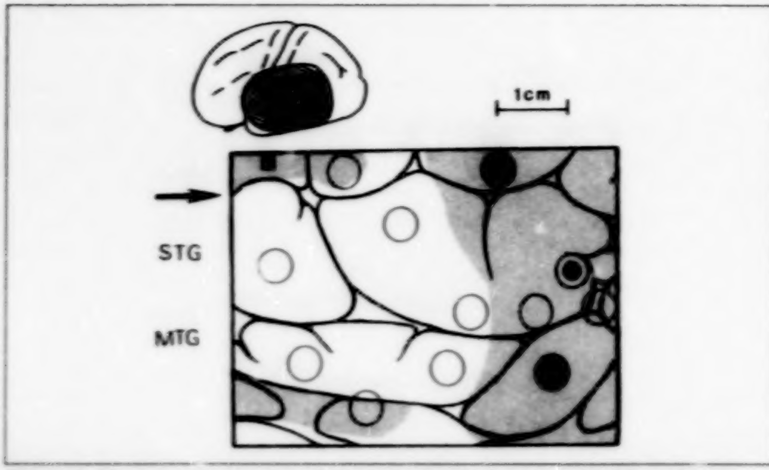

Figure 3. Illustrates the location of "intrinsic signal" changes, probably indicating where neurons are active during naming in a twenty-four-year-old male. Shaded areas are intrinsic signal changes. Circles are sites of stimulation. Filled circles are sites of repeated naming errors identifying essential language areas. A single dot marks the site of a single error. No errors occurred during stimulation of the remaining sites. M is motor cortex; STG is superior temporal gyrus; MTG is middle temporal gyrus; and an arrow indicates the Sylvian Fissure. (Redrawn from M. Haglund, G. Ojemann, and D. Hochman, 1992.)

guage cortex. The frontal slow potential is likely a premotor potential, for similar changes occur with overt speech. Its presence during silent naming is likely a sign of inner speech and indicates that all language processing includes activity in motor areas.

Brain wave studies are considered rather arcane in modern neuroscience, yet these studies not only have provided evidence for parallel processing in language cortex and activation of motor areas even in silent language but also provide some insight to mechanisms underlying language generation. Local desynchronization in animals can be elicited by activity of the thalamocortical activating system. We have previously shown that the human thalamus has a role in language. One mechanism probably involved in language generation is activity from the thalamus selecting the portion of the temporal cortex that must be active during the language task.

Activity in Nonessential Areas During Naming

Intraoperative optical imaging of the intrinsic signal is new. Few recordings of human brain activity during language have been analyzed. The great promise of this technique is its potential to screen the neocortex for activity of small aggregations of neurons,

thus providing clues to how widely distributed neuronal activity is during naming. Neuronal activity need not be confined to essential areas. Indeed, figure 3 illustrates the location of intrinsic signal changes recorded during naming from the posterior temporal cortex of the language-dominant hemisphere in one patient. The changes are confined largely to the posterior temporal lobe but extend more widely than the essential areas for naming identified by stimulation mapping in this same patient. Neuronal activity during language apparently occurs in parts of the temporal cortex that are not essential for language.

The analysis of microelectrode recordings of neuronal activity in nonessential cortex corroborates that finding. Electrical activity in neurons has two components: graded responses characterizing activity in dendrites (the input elements to nerve cells), which provide the basis for brain waves, and action potentials (the "all or none" output of a nerve cell that transmits information to other neurons over axons), which represent events recorded by microelectrodes. Ted Schwartz and I recently compared the change in frequency of action potentials recorded from 46 neurons in the nonessential temporal cortex during three conditions in response to the same visual cues: naming aloud, naming silently, and a spatial matching task. Twenty-five of these neurons were recorded from the nondominant right hemisphere, the remainder from nonessential areas of the left hemisphere. Even though these recording sites were not essential for language, 24 percent of the cells in the nonessentiual cortex showed significant changes in activity with overt or silent naming, with no significant differences in the number of cells in the left or right temporal lobes with these changes. Neurons that change activity with language seem to be widely distributed in either temporal lobe. Rather surprisingly, these changes in activity were usually linked to either overt or silent naming but not to both.

In these microelectrode recordings obtained during naming, features were identified that distinguished activity recorded from neurons in the left-language dominant temporal lobe from that recorded in the right nondominant side. The change in activity during language in the left (dominant) hemisphere was predominantly a reduction in activity, or relative inhibition. A possible explanation for this finding is that these recordings were made from an inhibitory surround. This result suggests that in the dominant hemisphere activity is focused by having increased neuronal activity, presumably a feature of essential areas, delineated by a band of surrounding inhibition extending into nonessential areas. Right,

nondominant hemisphere activity during naming was characterized by excitation.

Neurons can convey information to other neurons not only by changing the frequency of activity but by changing the pattern of activity, much as information is transmitted by FM radio. Only a few investigations of the changes in patterns of neuronal activity with language have been done, however. Professor N. P. Bechtereva and her colleagues at the Institute of Experimental Medicine in St. Petersburg, Russia, reported specific patterns of activity for specific words and semantic categories, in recordings from subcortical structures. The late Professor Otto Creutzfeldt and I identified repeatable patterns of activity related to specific words in recordings from the temporal cortex in two patients. In one patient, the repeatable pattern was present each time she heard a specific word, with a different repeatable pattern for another word. In the other patient, the pattern specific to a particular word was present both with listening to the word and repeating it aloud. A few neurons, then, may generate a particular pattern of activity to a particular linguistic element, but we do not know whether there are neurons that generate specific patterns when naming particular objects. Since activity showing specific patterns when perceiving specific words has been recorded, it seems likely that neurons also exist with specific patterns for particular objects.

Organization of Different Language Dimensions

These intraoperative investigations of naming provide an indication of the cortical organization underlying one language dimension. That organization includes neurons widely distributed and multiple highly localized essential areas across association cortex. The essential areas are confined to the dominant hemisphere and show high variability that is related, in part, to a subject's sex and verbal ability. Neurons and the multiple essential areas in the dominant hemisphere are activated in parallel. Activation is probably more intense in essential areas, with an inhibitory surround, reflecting activity of ascending thalamocortical activating circuits.

When these same intraoperative investigations are applied to other dimensions of language, many features of this organization can again be identified but here involving different neurons and different essential areas. Separate systems for many different dimensions of language may exist. Some of the most compelling evidence for this rather unexpected finding has come from our studies of naming the same pictures in two different languages in multilingual

patients. When Professor Harry Whitaker and I first investigated naming in two languages with the stimulation mapping technique, each patient demonstrated some separate essential sites for each language, a finding that has since been confirmed by other investigators. With Professor Bellugi's assistance, Mike Haglund and I investigated naming in English and American Sign Language (ASL) in a hearing patient who had learned ASL to communicate with a deaf relative. We identified sites essential for English and not ASL, other sites essential for ASL and not English, and one site where naming in both languages was intact; during stimulation, however, the patient could not interpret signs orally. Any changes on the few microelectrode recordings during naming in two languages are usually confined to only one of the languages. We have recorded neurons showing decreased activity with naming in English but not when naming the same pictures in Spanish. In a second patient, neurons increased activity with overt Finish naming but not with silent Finish naming or with overt or silent naming of the same pictures in English. We also have recorded a neuron that changed activity only with naming in English in the patient examined during ASL and English.

A similar picture emerges from investigations of naming and reading. Essential areas for naming or reading are often separate. In a stimulation mapping study of fifty-five patients, we analyzed the relation between essential areas for naming and reading simple sentences. At 61 percent of the sites with any change, only one of the two functions was altered. In twenty-nine neurons, we recorded activity in nonessential cortex during both naming and word reading. Nine neurons changed activity with one or the other linguistic function. Only one changed with both. Not only are the essential areas for these two functions separate, but so are the widely dispersed neurons that are part of each system.

Using the stimulation mapping technique in fourteen patients, we investigated the localization of essential sites for five different language dimensions: naming, sentence reading, phoneme identification, mimicry of orofacial speech gestures, and recent verbal memory. Sites where only one of these dimensions was altered were encountered frequently. In that context, combinations of changes at the same site were particularly instructive, providing insight to underlying functions of some areas. Figure 4 indicates sites exhibiting changes in different single functions or in particular combinations. One combination involved changes in all language output and the ability to mimic single speech gestures. This combination identifies a final motor output pathway for speech, a

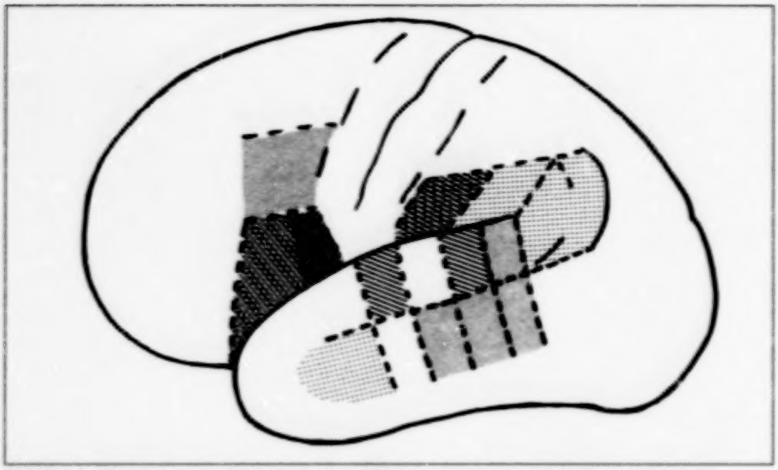

Figure 4. Illustrates essential areas for different language dimensions based on stimulation mapping during naming, reading, mimicry for speech gestures, phoneme identification, and recent verbal memory in fourteen patients. Zones where essential sites for different language dimensions are located are indicated by symbols: Single cross-hatching indicates motor speech functions; double cross-hatching marks a final motor speech pathway; dense stippling shows sites essential for naming alone or reading alone, the latter often involving grammatical aspects of language; and light stippling indicates sites essential for only recent verbal memory, which was intact in other areas. At most of the sites in the single or double cross-hatched areas, phoneme identification was also altered. In areas with both stippling and cross-hatching, separate sites showed either memory changes or motor speech changes but not both. (Redrawn from Ojemann, 1983.)

true Broca's area. As expected, this combination most often occurred at sites in the posterior inferior frontal cortex immediately in front of the face motor cortex. However, motor areas for language appear to extend well beyond this final output pathway. A second combination of changes occurring with stimulation of the same site included disturbances of naming, reading, and mimicry of sequences of orofacial speech gestures, but not of single gestures. Errors also were absent in the measure of recent verbal memory, indicating that cues for the tasks were perceived. This combination occurred at sites in the superior temporal lobe and the anterior parietal lobe, indicating that motor speech functions involve much of the peri-Sylvian cortex, a finding corroborating Jay Mohr's study of the location of strokes that produce permanent motor aphasias.

In that same study, phoneme identification was disturbed at most of the sites with motor speech changes. This was true even though this study exploited a special advantage of stimulation, that the blocking of cortical function can be turned on and off. In this

study the blocking current was applied only when the phoneme was heard.

There are several possible explanations for the finding that many of the same sites that are essential for speech production also are essential for speech sound identification. One explanation derived from the psycholinguistic studies of Professor Alvin Liberman and his colleagues at the Haskins Laboratory is that speech sound decoding involves creation of a motor output model of that sound, the "motor theory of speech perception." This theory predicts the combination of effects we observed, that altering motor speech function at a site should also disturb speech sound identification. Another explanation for the finding is based on the work of Paula Tallal and William Calvin. Their work suggests that precise timing underlies both speech production and speech perception, which are the functions we have altered, producing deficits in both.

Sites where only single functions were altered surround this peri-Sylvian area involved in speech production and perception (figure 4). Sites essential for only naming or only reading were closest to the peri-Sylvian area. The reading changes often involved the parts of sentences concerned with syntax, indicating that some of these sites have a special role in grammar. Sites essential for only recent verbal memory were further away from the peri-Sylvian area, in the frontal, temporal, and parietal lobes. This separation of recent memory and language mechanisms was clearly evident at some sites where stimulation repeatedly disturbed naming object pictures, but the same current at that same site had no effect on remembering that name, even when the current was applied at the time the name was produced from recent verbal memory.

Microelectrode recordings support many but not all of stimulation mapping findings that form the basis for figure 4. In our studies, neurons changing activity with speech production frequently have been recorded from superior temporal gyrus, supporting the wide extent of motor speech areas. In contrast to what we found in stimulation mapping, here neurons usually changed activity with only speech production or perception. Or, if they did change with both, it was in opposite directions, activated with one, but shut off with the other.

This result likewise occurs even though the same word is involved in production or perception, in one case spoken aloud by the patient and in the other by someone else. Apparently, the system for speech perception is briefly turned off when one speaks. Temporal cortical neuronal recordings frequently change activity with recent verbal memory measures especially at memory entry

and retrieval. Activity does not change when memory is stored during a distracting task. Neurons that change activity with recent memory rarely show changes with language measures. As we have seen, neurons rarely change activity with more than one language measure. An interesting side observation of these studies is that when activity of two nearby neurons is picked up by a single microelectrode, any changes in activity in those neurons are usually linked to different tasks.

A number of features of the cortical organization of language that do not fit the classical model of language organizaiton in the human brain emerge from the intraoperative studies reviewed here. Separate systems exist for many different dimensions of language, and each system includes localized essential areas. Essential areas related to motor speech functions are most often located in peri-Sylvian cortex of the frontal, superior temporal, and anterior parietal lobes. These same areas are often essential for decoding speech sounds, although the individual neurons within these areas are usually related to either speech production or speech sound identification but not both. Essential areas for specific language dimensions such as naming or reading surround this motor area. They in turn are surrounded by essential areas for recent verbal memory. Each system also includes neurons active only with that system but widely dispersed throughout the cortex, even in the nondominant hemisphere. Components of a system within the dominant hemisphere are activated in parallel. These findings require revision of the classical model of the organization of language in the human brain.

Suggested Readings

Creutzfeldt, O., G. A. Ojemann, and E. Lettich. 1989a. Neuronal activity in human lateral temporal lobe. I. Responses to speech. *Experimental Brain Research* 77:451–75.

Creutzfeldt, O., G. A. Ojemann, and E. Lettich. 1989b. Neuronal activity in human lateral temporal lobe. II. Responses to the subject's own voice. *Experimental Brain Research* 77:476–89.

Fried, I., G.A. Ojemann, and E.E. Fetz. 1981. Language-related potentials specific to human language cortex. *Science* 212:353–56.

Haglund, M.M., G.A. Ojemann, and D.W. Hochman. 1992. Optical imaging and epileptiform and functional activity in human cerebral cortex. *Nature* 358:668–71.

Haglund, M.M., G.A. Ojemann, E. Lettich, et al. 1994. Dissociation of cortical and single unit activity in spoken and signed languages. *Brain and Language* 14:19–27.

Ojemann, G.A. 1975. Language and the thalamus: Object naming and recall during and after thalamic stimulation. *Brain and Language* 2:101–20.

Ojemann, G.A. 1983. Brain organization for language from the perspective of electrical stimulation mapping. *Behavioral Brain Science* 6:189–230.

Ojemann, G.A. 1989. Some brain mechanisms for reading. In *Brain and Reading*, ed. C. Von Euler, I. Lundberg, G. Lennerstrand, 47–59. New York: Macmillan.

Ojemann, G.A., O. Creutzfeldt, E. Lettich, and M. Haglund. 1988. Neuronal activity in human lateral temporal cortex related to short-term verbal memory, naming and reading. *Brain* 111:1383–1403.

Ojemann, G.A., I. Fried, and E. Lettich. 1989. Electrocorticographic (ECoG) correlates of language. I. Desynchronization in temporal language cortex during object naming. *Electroencephalography Clinical Neurophysiology* 73:453–63.

Ojemann, G.A., and C. Mateer. 1979. Human language cortex: Localization of memory, syntax and sequential motor-phoneme identification systems. *Science* 205:1401–3.

Ojemann, G.A., J. Ojemann, E. Lettich, and M. Berger. 1989. Cortical language localization in left-dominant hemisphere. *Journal of Neurosurgery* 71:316–26.

Ojemann, G. A., and H. A. Whitaker. 1978. The bilingual brain. *Archives of Neurology* 35:409–12.

Penfield, W., and L. Roberts. 1959. *Speech and brain mechanisms.* Princeton: Princeton University Press.

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THE REPRESENTATION OF LEXICAL KNOWLEDGE IN THE BRAIN

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How is knowledge of language represented in the brain? To answer this question we must find some methodology that will allow us to investigate a property exclusive to human beings—only humans have a language faculty. Obviously, invasive methodologies used to explore the functional organization of the brain in nonhumans are not available to us. We must rely on other techniques. One such technique, used by cognitive neuropsychologists, is to infer the nature of normal human cognition from the impaired performance of brain-damaged patients. The inference procedure is as follows: The parts into which an impaired cognitive system breaks down are assumed to be the relevant units and subunits of normal processing. By analyzing the different forms of language impairment resulting from brain damage, we hope to reconstruct the internal organization of the normal language-processing system. This method was pioneered in the mid 1800s and has been refined over one hundred years of detailed observations of neurological disorders.

Several assumptions are required to support inferences about normal cognition from the study of cognitive disorders. Since this method relies on the detailed study of individual patients, we must assume the fundamental equivalence of normal human cognitive systems, i.e., despite the many individual differences that distinguish among people, the general structures of cognitive and linguistic processes are fundamentally identical across individuals. Second, we must assume that brain damage does not result in cognitive processes created de novo; that is, we must assume that the impaired system consists of specific deformations of the normal cognitive system. Finally, we must assume that the human cognitive system is sufficiently modular in its organization so that the effects of local brain damage will often have only relatively restricted

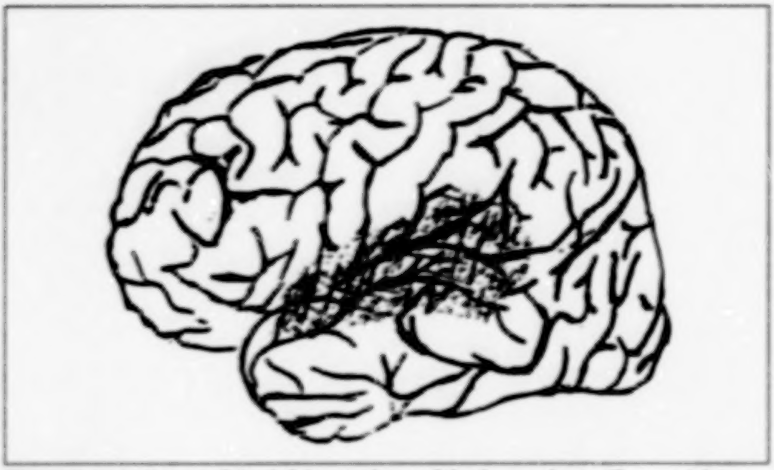

Figure 1. Lateral view of the left hemisphere of the human brain. The peri-Sylvian area is the shaded part.

effects on the cognitive system. For example, we assume that damage to the neural mechanisms underlying visual processes, say in reading, do not affect the organization and processing structure of the speech production system.

We have known for centuries that normal functioning of the language faculty depends crucially on the integrity of the left hemisphere of the brain. The beginning of modern human neuropsychology can be traced to the seminal work of the neurologists Paul Broca and Carl Wernicke in the second half of the nineteenth century. These pioneers of neuropsychology were the first to document and to interpret highly specific correlations between particular patterns of language impairment and restricted regions of the left hemisphere. Their work and that of many other neurologists who followed their pathbreaking research established two important facts: (1) the peri-Sylvian region of the left hemisphere is fundamental for normal language use (figure 1); and, (2) different parts of the language areas of the left hemisphere are implicated in different aspects of language processing.

Thus, Wernicke documented one of the most important dissociations of language processing following focal brain damage. He showed that lesions in the posterior/superior parts of the temporal lobe result in more severe language comprehension deficits than production deficits, whereas lesions in the posterior/inferior parts of the frontal lobe result in more severe difficulties in language production than in language comprehension. A major contribution of this

early work was the establishment of a fundamental principle that has guided modern neuropsychology: the modular organization of cognitive processes and the brain. Neuroscientists and cognitive scientists assume that cognitive abilities such as language, for example, are the result of the concerted activity of many simple processing mechanisms distributed in many different regions of the brain.

In the effort to chart the functional organization of the human brain, modern cognitive neuropsychology has been influenced not only by the results of classical neuropsychology but also by recent developments in the cognitive sciences—such as cognitive psychology, linguistics, and artificial intelligence. The result has been an important shift of focus in the type of questions addressed in neuropsychological research and major accomplishments in our understanding of the nature of cognitive deficits following brain damage. The emphasis is no longer on the correlation between gross behavioral deficits (for instance, disorders of language comprehension) and locus of brain damage but rather on the relationship between the cognitive mechanisms underlying a particular cognitive ability (for instance, the set of operations that underlie our ability to understand sentences) and the affected brain structures.

To give just one example, in the mid-seventies my colleague Edgar Zurif (Brandeis University, Boston) and I were able to show that failure in sentence comprehension can result either from damage to lexical processes (our knowledge of words) or from damage to syntactic processes (our knowledge of the relationships between words in sentences). Specifically, we showed that brain damage can disrupt syntactic processes selectively while leaving the ability to understand the meaning of words unimpaired. By syntactic processes I mean those processes that concern the ways in which words are organized in a sentence. Syntactic knowledge allows us to know, for example, that the sentence *Mary is chasing John* means something quite different from *Mary is being chased by John* or *John is chasing Mary*. The difference in meaning among the three sentences is carried by the grammatical relations that exist among the words in the sentences. This knowledge can be disrupted independently of the knowledge about the individual words that make up a sentence.

In our original experiments, which have since been replicated in many subsequent experiments by other investigators, we showed that some brain-damaged patients could understand the meaning of the words in a sentence but failed to understand the meaning of the sentence as a whole. For example, a patient might understand the meaning of *dog, cat, chases,* and *black* in *The dog*

that the cat chases is black but fail to understand that the cat is doing the chasing and the dog, not the cat, is black.

The fact that syntactic knowledge can be disrupted independently of lexical knowledge suggests the hypothesis that these two kinds of linguistic knowledge are subserved by distinct neural structures or processes. In our original experiments as well as in later research, the evidence favored the view that normal syntactic processing is dependent on the integrity of neural structures in the frontal/temporal parts of the left hemisphere, whereas the meaning of words seems to be represented in the temporal/parietal regions of the left hemisphere. But, even this more detailed view of the functional organization of the human brain is too simple. This view is inadequate both for the psycholinguist interested in the cognitive mechanisms underlying language use and for the neuroscientist interested in the functional organization of the human brain. In fact, recent investigations of the many forms of language impairment following brain damage allow us to make more precise statements about the organization of language in the brain, at least with respect to the functional distinctions that must be captured at the neural level. To illustrate the latter type of research and the inferences it can support, I will focus on a relatively narrow aspect of language processing: the use of single words in such tasks as naming, oral reading, and writing.

We need to clarify some fundamental distinctions when talking about lexical knowledge. The most important distinction is between knowledge of the meaning of a word and knowledge of the form of a word. Consider the common word *cup*. You know that the word *cup*—the sound /kʌp/ and the letter sequence <c> <u> <p>—refers to an object used for drinking (the concept *cup*). The relationship between the form of a word and the concept it refers to in a language is completely arbitrary. A person who speaks and reads English, or any other language, must have three distinct types of knowledge. They must know the sound (phonology), the spelling (orthography), and the meaning (semantics) of words. We will refer to the memory systems that store these three types of knowledge as the phonological lexicon, the orthographic lexicon, and the semantic component, respectively.

There is overwhelming evidence that these three types of knowledge of words are represented independently in the brain. This notion is represented schematically in figure 2. The figure illustrates the hypotheses that to be able to pronounce a written word, for example, *tulip*, you must be able to recognize it as the word composed of the letter sequence <t> <u> <l> <i> <p>; you must un-

derstand what it means; and then you must be able to produce the sound /tulip/. Similarly, when we hear the word /tulip/ we must recognize the sound, understand its meaning, and, if we are asked to write the word, we must then access knowledge of how the word is spelled in order to be able to write it correctly. These kinds of knowledge can be damaged selectively. There is evidence that the representation of our knowledge of what a word means can be damaged, while the representation of the phonological and orthographic forms of a word may be spared, and vice versa. There is also evidence that the phonological form and the orthographic form of a word can be damaged independently of one another.

One type of error not infrequently observed in patients with brain damage is the production of semantic paraphasias—the production of a semantically related word instead of the correct response. For instance, the patient may produce "orange" in response to a picture of a banana. Semantic errors are sometimes also produced in oral reading (semantic paralexias) and in writing (semantic paragraphias) tasks. What could be the basis for such errors? What does their occurrence tell us about the organization of lexical knowledge in the brain?

My colleague Argye Hillis (Johns Hopkins University, Baltimore) and I have been able to show that not all semantic errors have the same underlying cause. The investigation of the different causes of semantic errors can help reveal important properties about the organization of the lexical system. In this regard, the pattern of semantic errors produced by four aphasic patients—KE, RGB, HW, and SJD—we have recently studied is particularly instructive. All four patients produced semantic errors in lexical processing tasks. They produced errors such as ***quill*** → "feather" and ***diamond*** → "pearls" by RGB, ***tragic*** → "sad" and ***fabric*** → "dress" by HW, ***elbow*** → "foot" and ***apple*** → "orange" by KE, and ***hurry*** → "run" and ***peel*** → "strip" by SJD. The patients differed, however, in terms of which tasks gave rise to the production of semantic errors.

Patient KE sustained damage to the fronto-parietal region of the left hemisphere as a consequence of a thromboembolic stroke. He made semantic errors in ***all*** lexical comprehension and production tasks; he made semantic errors in oral reading, in writing to dictation, in oral and written naming of visually and tactilely presented objects, and in matching a spoken or written word to a picture. Table 1 presents examples of KE's responses in four lexical production tasks. The important point here is that he made semantic errors both in oral production as well as in written production tasks. The implication of this pattern of results is that the patient has sustained damage to the se-

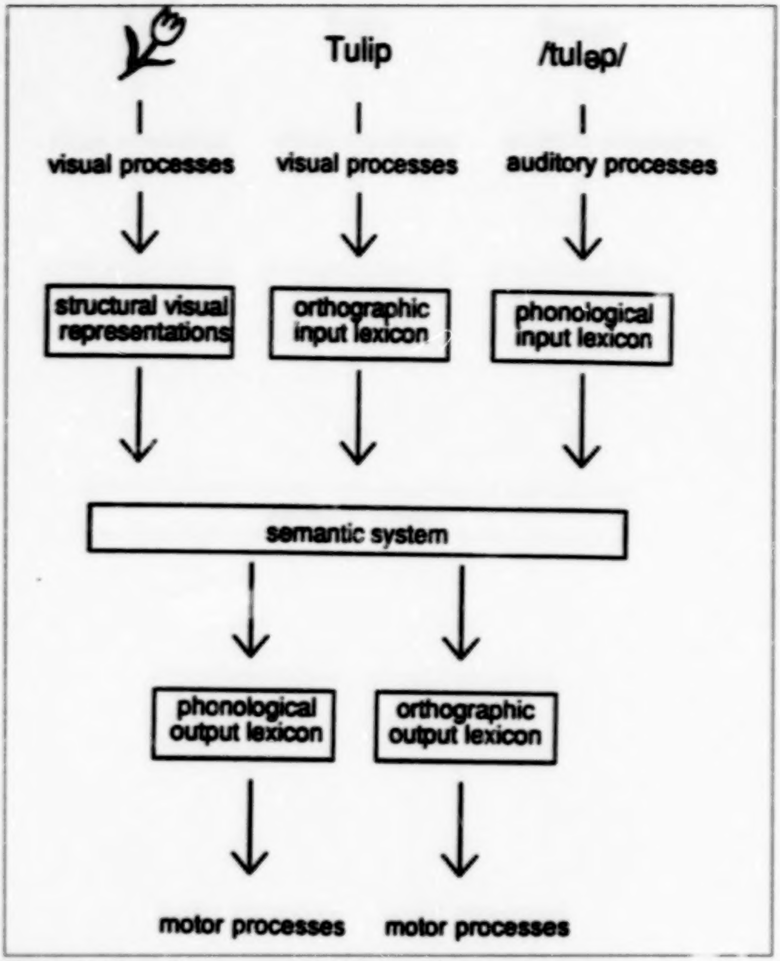

Figure 2. Schematic representation of the lexical processing system.

mantic component of the lexical system—the only component of processing which if damaged would lead to the observed co-occurrence of semantic errors in all lexical processing tasks.

Now compare KE's pattern of performance with that of RGB and HW. The latter two patients also sustained damage to the left hemisphere. RGB's lesion involved the fronto-parietal area, whereas HW's lesions involved the parietal and the occipital lobes. As already noted, both patients produced semantic errors; however, they produced these errors only in tasks requiring an oral response, for example on tasks of oral reading and oral picture naming. As may

Table 1
Examples of KE's Responses In Several Tasks

Stimulus	*Oral reading*	*Oral naming*	*Written naming*	*Dictation*
arm	ear	finger	leg	hand
elbow	foot	leg	leg	leg
stomach	belly	belt	wrist	belt
frog	lizard	turtle	+	turtle
shelf	lamp	chair	light	lamp
sock	+	gloves	mittens	mitten
jacket	+	belt	sweater	sweater

+ signifies the correct response

be seen from the examples in table 2, although RGB and HW made errors both in tasks involving spoken as well as written output, they did not make semantic errors in writing to dictation or in written naming. In other words, RGB and HW demonstrate a dissociation between the ability to retrieve the phonological and the orthographic forms of a word. They cannot retrieve the phonological form of a word but they can retrieve its orthographic form (although they then make spelling errors because of other processing difficulties not relevant to the present discussion). This pattern of performance suggests that only the phonological forms of words are damaged in RGB and HW but not the semantic representations.

Consistent with this account of the underlying causes of the patients' impairment and, in contrast to KE, RGB and HW did well on tasks of word comprehension, implying that their semantic representations of words are intact. For example, when RGB was asked to read aloud the word *records* he responded "radio" but then went on to define the stimulus word as: "You play 'em on a phonograph... can also mean notes you take and keep." Similarly, HW read *diamond* as "ring" but defined the stimulus as: "A stone from Africa, from the earth; used for making records, and for jewels." These are reasonable definitions of the words *records* and *diamond*.

Other examples of dissociation between comprehension and production are represented in table 3. RGB and HW appear to understand correctly the stimulus words they are unable to produce in an oral reading task, and they can produce in the stimulus word writing. The implication of this pattern of performance is that their

Table 2
Definitions of Words Following Semantic Errors

Patient RGB

Stimulus	*Response in oral reading*	*Definition of the stimulus the patient was unable to pronounce*
records	radio	You play 'em on a phonograph . . . can also mean notes you take and keep.
necklace	necktie	You would wear; a woman would have around her neck . . . made out of metal . . . gold or silver.
quill	feather	They're long and have a point . . . animals, porcupines have them.
volcano	lava	Fire come out of it . . . a big thing . . . a mountain.
worthless	value	Not worth anything . . . useless.
duplication	photograph	You make a copy of it

Patient HW

Stimulus	*Response in oral reading*	*Definition of the stimulus the patient was unable to pronounce*
pirate	money	Has a thing over it's eye . . . I would say they don't gave any more, but they do in business. He wants your money and your gold.
instinct	think	Something that you don't learn, can't, but you know anyway. Its not nice to say, but woman have it better than men.
igloo	cold	People far away . . . way up there . . . sleep in it. It's their home.
fluid	drink	Anything that would be something you drink.
diamond	ring	A stone from Africa, from the earth; used for making records, and for jewels.

"semantic" errors are the result of failure to retrieve the correct phonological representation for production because of damage to the phonological output lexicon.

Patients also have been reported who show the opposite dissociation: production of semantic errors only in written production tasks. Patient SJD made semantic errors in tasks requiring written output but did not make semantic errors in oral production tasks. Furthermore, like RGB and HW, SJD performed well on tasks of comprehension, indicating that her semantic component was not affected by brain damage. This patient's pattern of performance

Table 3
Examples of RGB's and HW's Errors in Oral and Written Production Tasks

RWB	*Stimulus*	*Oral reading*	*Oral naming*	*Written naming*
	sock	stocking	mitten	sock
	cap	hat	stocking	cap
	kangaroo	giraffe	raccoon	ka g oo
	donkey	monkey	monkey	dokey
HW				
	lime	lemon	melon	lime
	jar	lunch	bottle	jar
	octopus	clam	squid	octop
	shelf	top	book	shef

suggests that the cause of her semantic errors is damage to the orthographic output lexicon.

The performance of patients KE, HW, RGB, and SJD provides evidence that knowledge of the meaning of words is represented in the brain independently from knowledge of the phonological and of the orthographic forms of words. Thus we have empirical evidence in favor of the model of lexical processing schematically depicted in figure 2 which shows the semantic lexicon, the phonological output lexicon, and the orthographic output lexicon as autonomous processing components. These independent components of lexical representation can be impaired selectively by brain damage, resulting in the observed patterns of association

(patient KE) and dissociations of symptoms (patients RGB, HW, and SJD).

As remarkable as these dissociations of symptoms are, there are even more startling reports of dissociations of symptoms that concern only part of one component of the lexical system. These patterns of performance have helped reveal aspects of the internal organization of the semantic, phonological, and orthographic components of the lexical system. One rather striking result is the observation, first reported by Professor Warrington of the National Hospital, London, and her collaborators, of category-specific deficits. These investigators observed that some patients have difficulty naming the members of some categories but not those of other categories. The most celebrated category-specific dissociation concerns the selective impairment of the categories living versus nonliving things. Thus, there are reports of brain-damaged patients who may have difficulty naming common living things, such as dog, apple, eagle, rose, or carrot, but who show no difficulty naming even rare artefacts, such as sextant, calipers, or sphinx. Conversely, patients have been reported who are selectively impaired in the ability to name common artefacts such as desk, car, or pencil but demonstrate no difficulty in naming members of the category of living things.

Category-specific deficits can be even more fine-grained than the living/nonliving distinction. Argye Hillis and I reported the performance of two brain-damaged patients, JJ and PS, both of whom sustained damage to the left temporal lobe, and exhibited contrasting category-specific deficits. Patient PS was selectively impaired in naming animals and vegetables, and patient JJ was impaired in naming all categories tested except animals. These two patients' contrasting patterns of category-specific deficits are reflected in table 4, which reports their respective percentages of correct responses in naming members of various categories. Patient JJ was impaired in naming fruits, vegetables, foods, body parts, clothing, furniture, and other categories but was remarkably unimpaired in naming members of the category animals. For example, when JJ was asked to define the word *lion* he responded, "A large animal about four feet tall, maybe taller at the shoulders. It has a long body and very large paws and stands on all four legs. It has a monstrous head with which it growls and it has a mane, a large body of hair. It lives in Africa." JJ defined *heron* as, "This bird has a long neck and legs. It lives near water. Stands in the water . . . very tall—may be about six feet . . . not brown, but white and blue perhaps."

These rather complete definitions for animals contrast sharply with his definition of *bench*: "It's a devise you sit on, about

twelve inches high with four legs; it revolves you around while you're sitting. It can be made of metal or wood." This is clearly a definition of a *stool*, not a *bench*. The reverse pattern of impaired and unimpaired categories was observed for patient PS. His naming and comprehension difficulties were essentially restricted to the category of animals. For example, PS defined *heron* as "A fish" but gave a reasonably accurate description of *ottoman*: "A chair without a back that you put your feet on."

One implication of these and related results is that our knowledge of the meaning of words is represented in some orga-

Table 4

Category-Specific Deficits in Naming

	Number of Stimuli	*Test Sessions* 1	2	3	4	5	6	7
JJ								
All Animals	(46)	91	85	72	80	76	74	92
Nonanimals	(98)	12	14	14	11	12	7	17
PS								
All Animals	(46)	39	39	39	41	37	48	72
Nonanimals	(98)	80	83	83	84	87	87	89

nized fashion. The exact nature of that organization, however, is still not known. Perhaps the lexical semantic component is organized into categories corresponding to those of folk taxonomy (such as, land animals, fruits, and so on). An alternative hypothesis is that category-specific deficits reflect the underlying similarity shared by members of semantic categories. That is, if the meaning of words were to be represented in terms of sets of semantic features (for example, edible, animate, male, young, and so forth), then damage to specific sets of features would result in selective damage to all concepts sharing those features. Since members of a category are likely to share many semantic features, one consequence of damage to some of those features would be the occurrence of category-specific impairments. At the present time we cannot distinguish between these two hypotheses. Nonetheless, it is

clear that semantic information is organized in the brain in such a way as to reflect categorical relations among words.

Our knowledge of words also is organized relative to their grammatical class membership. Knowledge of function words and grammatical morphemes (for instance, auxiliary verbs, prepositions, tense, and number inflections) can be damaged independently of knowledge about content words (nouns, verbs, and adjectives). A typical utterance produced by some patients may take the following form: "Mother washing sink ... water flowing floor ... running water ...," in which function words and grammatical morphemes are often either absent or incorrect. In the sixties and seventies, Professor Goodglass of the Boston Veterans Administration Hospital, and his collaborators, and subsequently many other researchers, clearly documented that some brain-damaged patients show particular difficulties in producing and comprehending function words relative to other classes of words. The selective impairment of a grammatically defined class of words indicates that grammatical information may constitute the basis for the organization of lexical information at some level of the lexical processing system.

An important source of evidence concerning the role of grammatical class in the organization of lexical knowledge in the brain concerns the reported dissociations in processing nouns versus verbs. Some years ago, my colleague Gabriele Miceli at the Università Cattolica in Rome and I were able to show that patients who have disproportionate difficulties producing verbs as opposed to nouns tend to have sustained damage to anterior regions of the language area, whereas those patients who show disproportionate difficulties in producing nouns tend to have lesions in the posterior regions of the language area. These results, however, did not permit precise identification of the level or levels within the lexical system where grammatical information is represented. The fact that some patients show selective difficulty with one grammatical class in all lexical processing tasks suggests that grammatical distinctions are represented at the level of the lexical semantic component. Evidence also suggests that such distinctions are represented in the phonological and orthographic lexicons. The performance of patients HW and SJD, described above, is important in this regard.

As noted previously, HW presented no difficulty writing words (on tasks of writing to dictation and written naming), but when she was asked to read aloud or name pictures, her performance was impaired. Her oral production difficulties were disproportionately severe for verbs as compared to nouns. Patient SJD also demonstrated disproportionate difficulty with verbs, but in

tasks requiring written, rather than oral production. SJD's difficulty in writing verbs is well illustrated by the diary she kept as part of her speech therapy program. The diaries consist of text interspersed with semantic errors or blanks for the verbs she could not write. For example, one entry is as follows: "I will_____the maid for dinner. Greg is picky about food. Andy is worse. They____for pizza and turkey." But she had no trouble in orally producing the verbs she could not write, as indicated by the way she read her diary entry: "I will *play* the maid for dinner. Greg is picky about food. Andy is worse. They *ask* for pizza and turkey."

These two patients' difficulty in producing verbs in one modality of output was not simply because the verb stimuli used in the experiments were somehow more difficult than the nouns. This alternative explanation was ruled out by having the patients read aloud and write to dictation homonyms (for instance, *watch*), once as nouns (*the watch*) and once as verbs (*to watch*). For this purpose we constructed pairs of sentences that contained a word, such as *crack*, which can be a noun or a verb, and asked the patients, on separate occasions, to read and write the homonyms. For example, we read aloud to the patients the sentence, "There's a crack in the mirror," and then asked them to write the word *crack* in the space provided in the sentence frame in which the target word was missing: "There's a_______in the mirror." On another occasion we read aloud the sentence, "Don't crack nuts in here," and asked them to write the word *crack* in the appropriate space in the sentence frame: "Don't_______nuts in here." The reading task with homonyms involved having the patients read aloud, on separate occasions, the underlined words in the sentences, "There's a *crack* in the mirror," and, "Don't *crack* nuts in here." Despite the fact that the spoken and written responses were identical for the noun and verb forms, the two patients showed considerably greater difficulty in reading (HW) and writing (SJD) the verb form of the homonyms.

The performance of a third patient, EBA, is of interest because she shows the opposite pattern of performance to that reported for HW and SJD. This patient had far greater difficulty in the oral production of nouns than verbs. A typical example of her speech is as follows: "Oh lordy, she is making a mess. She let the thing go, and it's getting on the floor. They're stealing something. He's falling. He's gonna hurt himself. She's [pointing to a picture of a woman] cleaning these things. She's [pointing to girl] looking at him falling, and she's gonna get some of the stuff he's giving her." EBA tended to use words like *thing*, *something*, and pronouns in the place of nouns which she could not produce. She had no difficulty

producing verbs. In controlled experiments where she was asked to produce a word (a homonym) in response to a definition, EBA correctly produced the target word when it was used as a verb but not when it was used as a noun. For example, in response to the definition, "What you do when you roll a ball down an alley to hit pins," she correctly said *bowl*; however, she could not produce *bowl* when given the definition, "A dish you use to eat soup or cereal." EBA's pattern of performance is difficult to square with claims that the noun/verb dissociations reported earlier were simply an effect resulting from verbs being inherently more difficult to use than nouns.

Of particular interest is the fact that these three patients' grammatical class effects were modality-specific. That is, they concerned only one modality of output— either oral or written production. The modality-specific character of these grammatical class effects locates the source of the impairment to the phonological (HW and EBA) and the orthographic (SJD) output lexicons. We are led to conclude that grammatical distinctions are represented not only at the level of the lexical semantic component but also at the level of the phonological and the orthographic lexicons.

The results I have reviewed here have important implications for theories of the functional organization of the human brain. Although we do not at present know the exact relationship between cognitive mechanisms and brain structures, the results suggest that distinct neural mechanisms are dedicated to processing different aspects of lexical knowledge—there is a module dedicated to representing lexical semantic knowledge, and there are other modules dedicated to representing the phonological and the orthographic forms of words. Within these large, complex processing units further subdivisions exist in terms of the grammatical class of words. The grammatical distinctions we have noted appear to be distributed along the anterior/posterior axis of the language area.

It probably does not require saying that the type of conclusions that can be reached about cognition-brain relationships from the study of the performance of brain-damaged patients are limited by the fact that we are dealing with experiments of nature where the type and size of lesions is beyond the control of the experimenter. Furthermore, it is a well known clinical fact that stable functional deficits are usually associated with fairly large lesions, making the task of fine-grained mapping between cognitive mechanisms and brain structures very difficult indeed. Nonetheless, such studies provide the basis for biologically motivated hypotheses about the organization of the lexical processing system. Although we still do not know how the brain represents the modular struc-

ture of the lexical system and its internal organization, we can be confident that some such structure is represented in the brain.

In conclusion, although I have presented the analysis of the performance of brain-damaged patients from the perspective of what it can teach us about the organization of language in the brain, we must not forget that this research has important clinical implications for understanding other cognitive disorders and the nature of language. If we are to make progress in developing increasingly successful therapeutic techniques aimed at helping aphasic and other cognitively impaired patients, we must have a deeper understanding of the nature of these disorders and the mechanisms of recovery. Research with brain-damaged patients not only provides a window into the structure and organization in the brain of normal language processes but also creates a foundation for therapeutic advances in this field.

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Suggested Readings

Caplan, D. 1992. *Language: Structure, processing, and disorders.* Cambridge, Mass.: MIT Press.

Caramazza, A. 1988. Some aspects of language processing revealed through the analysis of acquired aphasia: The lexical system. *Annual Review of Neuroscience* 11:395–421.

Caramazza, A., and A.E. Hillis. 1991. Lexical organization of nouns and verbs in the brain. *Nature* 349:788–790.

Damasio, A.R., and H. Damasio. 1992. Brain and language. *Scientific American* 267:88–95.

Ellis, A.W. and A. Young. 1988. *Human cognitive neuropsychology.* London: Lawrence Erlbaum Association.

Hillis, A.E., and A. Caramazza. 1991. Category specific naming and comprehension impairment: A double dissociation. *Brain* 114:2081–94.

McCarthy, R.A., and E.K. Warrington. 1990. *Cognitive neuropsychology: A clinical introduction.* San Diego: Academic Press, Inc.

Shallice, T. 1988. *From neuropsychology to mental structure.* Cambridge: Cambridge University Press.

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